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

DRAFT GUIDANCE

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For questions regarding this draft document, contact Jeffrey Murray at 301-796-1500.

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

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Revision 2

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7
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

14
15
16
17 **I.   INTRODUCTION**
18
19 The purpose of this guidance is to assist sponsors in the clinical development of direct-acting
20 antiviral (DAA) drugs for the treatment of chronic hepatitis C (CHC) from the pre-
21 investigational new drug application (pre-IND) through the new drug application (NDA) and
22 postmarketing stages.[2] For the purposes of this guidance, we define direct-acting hepatitis C
23 virus (HCV) antivirals as drugs that interfere with specific steps in the HCV replication cycle
24 through a direct interaction with the HCV genome, polyprotein, or its polyprotein cleavage
25 products. Specifically, this guidance addresses the FDA's current thinking regarding the overall
26 development program and clinical trial designs to support DAA drugs. This draft guidance is
27 intended to serve as a focus for continued discussions among the Division of Antiviral Products
28 (DAVP), pharmaceutical sponsors, the academic community, and the public.[3] The organization
29 of the guidance parallels the development plan for a particular drug or biologic.
30
31 This guidance does not address the development of drugs that target host functions necessary for
32 viral replication or immune-based drugs for the treatment of HCV infection such as new
33 interferon (IFN) drugs. Treatment of acute hepatitis C or therapeutics without antiviral
34 mechanisms intended to mitigate or reverse clinical or pathophysiological outcomes of CHC,
35 such as prevention of hepatocellular carcinoma (HCC) or reversal of fibrosis, are also not
36 addressed in this guidance. The main focus of this guidance is on development of DAAs as part
37 of IFN-free regimens. Because there are currently safe and highly effective FDA-approved IFN-

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

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

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

38 free treatment options, the DAVP recommends against studying an IFN-containing regimen in a
39 DAA treatment-naïve population.
40
41 Additionally, general issues of statistical analyses or clinical trial design are not addressed in this
42 guidance. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles*
43 *for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*,
44 respectively.[4] This guidance also does not contain details regarding nonclinical safety and
45 toxicology studies unless specific to HCV drug development. Such studies for direct-acting
46 HCV antivirals generally should be conducted in standard animal models as described in the
47 guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.
48
49 This guidance revises the revised draft guidance for industry *Chronic Hepatitis C Virus*
50 *Infection: Developing Direct-Acting Antiviral Drugs for Treatment* issued in October 2013.
51 Significant changes in this revision include:
52
53 - Modification of several sections to focus on IFN-free DAA regimens.
54
55 - Additional details on phase 2 and phase 3 trial design options for the evaluation of IFN-
56   free regimens in treatment-naïve and treatment-experienced populations, including DAA-
57   experienced populations. Specifically, this guidance recommends that each marketing
58   application contain at least one active-controlled comparative trial.
59
60 - Additional clarification on DAA drug development in specific populations including trial
61   design options for human immunodeficiency virus-1 (HIV-1)/HCV co-infected patients,
62   patients with advanced chronic kidney disease (CKD), patients with decompensated
63   cirrhosis, patients either pre- or postliver transplantation, and patients who failed to
64   respond to a prior DAA-based regimen.
65
66 Sponsors considering development of antiviral drugs for the treatment of CHC are encouraged to
67 communicate with the FDA through the pre-IND consultation program.[5] Pre-IND consultation
68 with the FDA is optional, although it may be particularly helpful for sponsors with limited
69 experience in the IND process or with unusual drugs or treatment approaches.
70
71 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
72 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
73 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
74 the word *should* in Agency guidances means that something is suggested or recommended, but
75 not required.
76

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

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

77
78 **II.   BACKGROUND**
79
80 HCV is a small positive-strand ribonucleic acid (RNA) virus in the *Flaviviridae* family. There
81 are at least seven different HCV genotypes, numbered 1 to 7; most genotypes have been divided
82 into multiple subtypes (e.g., genotype 1 subtypes 1a and 1b) (Smith, Bukh, et al. 2014). In the
83 United States, genotype 1 is the most common (70 to 80 percent), followed by genotypes 2 and
84 3. The remaining genotypes occur uncommonly in the United States, but may predominate in
85 other parts of the world (Gower, Estes, et al. 2014).
86
87 In the United States, approximately 3 million people have chronic HCV infection (i.e., CHC)
88 (Armstrong, Wasley, et al. 2006; Klevens, Dale, et al. 2012). CHC causes cirrhosis and HCC
89 and is currently the most common reason for liver transplantation in the United States. By 2007,
90 there were more yearly deaths in the United States related to HCV than HIV (Ly, Xing, et al.
91 2012).
92
93 The ultimate goal of CHC treatment is to reduce the occurrence of end-stage liver disease and its
94 complications including decompensated cirrhosis, liver transplantation, and HCC. However,
95 because progression of liver disease occurs over a long period of time, clinicians use sustained
96 virologic response (SVR), defined as lack of detection of HCV RNA in blood several months
97 after completing a course of treatment, to determine treatment success. SVR is considered a
98 virologic cure (Shiratori, Ito, et al. 2005; Singal, Volk, et al. 2010).
99
100 Total duration of treatment and choice of regimen may depend on HCV genotype or subtype and
101 disease factors such as the HCV RNA level or the presence or absence of cirrhosis. For many
102 years, the standard of care for treatment of CHC had been a combination of pegylated interferon
103 alpha-2 (peg-IFN) and ribavirin (RBV) administered for 24 (genotypes 2 and 3) or 48 weeks
104 (genotype 1 and others). The addition of a DAA (e.g., HCV protease inhibitor) to peg-IFN and
105 RBV substantially increased SVR (Casey and Lee 2013). Currently, the ability to achieve SVR
106 rates exceeding 90 percent using only DAAs (without IFN) in many populations of HCV-
107 infected patients has been well established. Throughout this guidance, antiviral treatment
108 *efficacy* refers to SVR assessed 12 weeks following cessation of treatment (SVR12).
109
110
111 **III.   DEVELOPMENT PROGRAM**
112
113   **A.   General Drug Development Considerations**
114
115 In addition to nonclinical development and early phase drug development, an overall drug
116 development approach with respect to target population, efficacy, and safety is addressed in the
117 following sections.
118

119   *1.   Nonclinical Virology Development Considerations*
120
121   Information about pre-investigational new drug testing and information regarding appropriate
122   nonclinical assays is available from the FDA.[6] Virology development for HCV DAAs should
123   follow existing guidance for drug development.[7] Additional recommendations for nonclinical
124   and clinical virology specific to the development of HCV DAAs are summarized throughout this
125   guidance.
126
127   a.   Mechanism of action
128
129   The mechanism by which a DAA exhibits anti-HCV activity should be investigated in studies
130   that include evaluation of the effect of the drug on relevant stages of the virus life cycle.
131   Mechanism of action investigations should include appropriate controls for assessing the
132   specificity of anti-HCV activity, which may include assessments of activity against unintended
133   HCV target proteins, related host proteins, or other viruses.
134
135   b.   Antiviral activity in cell culture
136
137   The antiviral activity of an investigational drug should be characterized in cell culture to
138   demonstrate activity and identify a preliminary target concentration for evaluation in HCV-
139   infected patients. Antiviral activity of candidate drugs targeting nonstructural components
140   should be assessed using HCV replicon systems, and 50 and 90 percent effective concentrations
141   (EC_{50} and EC_{90}) determined. We recommend evaluation of the drug's antiviral activity at
142   different concentrations of human serum and extrapolation to a 100 percent human serum-
143   adjusted EC_{50} value. The antiviral activity of drugs that target HCV entry functions can be
144   evaluated using HCV pseudoparticle systems. Assessments of antiviral activity against HCV
145   grown in cell culture are recommended for any anti-HCV drug when appropriate.
146
147   Cell culture studies should include assessments of antiviral activity against the major U.S. HCV
148   genotypes and subtypes and those for which an indication will be sought. We also recommend
149   assessments of antiviral activity against replication models using HCV components derived from
150   multiple clinical isolates because antiviral activity can vary for strains within each subtype. If
151   sponsors observe differences in susceptibility for different clinical isolates within the same viral
152   genotype or subtype, they should conduct additional genotypic and phenotypic characterizations
153   to identify genetic polymorphisms that may affect HCV susceptibility to the drug.
154
155   c.   Cytotoxicity and mitochondrial toxicity
156
157   The cytotoxic effects of the drug should be quantified directly in the cells used for assessing anti-
158   HCV activity, and a 50 percent cytotoxic concentration (CC_{50}) and therapeutic index should be

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[6] See the following FDA Web page:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplicati
ons/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm.

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

159 calculated (CC_{50}/EC_{50}). Cytotoxicity also should be assessed using various cell lines and
160 primary cells cultured under proliferating and nonproliferating conditions. Nucleos(t)ide analog
161 polymerase inhibitors should be assessed for bone marrow precursor cell toxicity with
162 appropriate controls. Mitochondrial toxicity should be assessed in glucose-containing and in
163 galactose-containing medium (i.e., Crabtree effect; Marroquin, Hynes, et al. 2007).
164 Mitochondrial assessments include assessments of mitochondrial toxicity, viability, function,
165 structure, and apoptosis in multiple cell types (e.g., assessing mitochondria copy number,
166 mitochondrial DNA, cell growth, cell protein, adenosine triphosphate content, oxidative
167 phosphorylation, lactase release). Inhibition of mitochondrial RNA polymerase also should be
168 evaluated for nucleos(t)ide analogs (Arnold, Sharma, et al. 2012). Positive controls for
169 mitochondrial toxicity studies should be relevant to the class of the investigational drug
170 whenever possible.
171
172   d.   Antiviral activity in animal models
173
174 In general, studies of anti-HCV activity in an animal model are not needed. However, if such
175 studies are conducted and provided in support of an anti-HCV therapy program, reported data
176 should include the HCV genotype/subtype used, time course plots of viral load data for each
177 animal, and an assessment of resistance development that includes monitoring the persistence of
178 resistant virus in the absence of anti-HCV treatment.
179
180   e.   Combination antiviral activity
181
182 Most, if not all, HCV DAAs will be used to treat CHC in combination with other anti-HCV
183 drugs. Early in development, cell culture combination antiviral activity relationships of the
184 investigational drug and other drugs anticipated to be used in combination should be
185 characterized to determine whether or not the combination antiviral activity is antagonistic. For
186 all combination antiviral activity assessments, sponsors should provide combination index values
187 when the two drugs are combined at or near their individual EC_{50} values, and studies should
188 include controls for cytotoxicity and antagonism (Coelmont, Paeshuyse, et al. 2006).
189 Combination antiviral activity relationships for HIV and HCV drugs with similar mechanisms of
190 action (e.g., HIV nucleos(t)ide analogue reverse-transcriptase inhibitors and HCV nucleos(t)ide
191 analogue NS5B polymerase inhibitors) also should be assessed before testing combinations of
192 the drugs in HIV-1/HCV co-infected patients.
193
194   f.   Resistance and cross-resistance
195
196 The ability of HCV to develop resistance to a DAA when subjected to drug selection should be
197 examined in appropriate cell culture models. Amino acid or nucleotide substitutions associated
198 with the development of resistance to the investigational drug should be determined and
199 validated by introducing the changes into the HCV genome and determining the conferred fold-
200 shift in susceptibility (based on EC_{50} and EC_{90} values) using cell culture or biochemical assays.
201 Results from these studies should be used to: (1) characterize the genetic barrier for resistance;
202 (2) predict whether a clinically achievable concentration of the investigational drug can reduce
203 the enrichment of drug-resistant viral populations; (3) identify potential resistance pathways; and
204 (4) support the drug's hypothesized mechanism of action. The *resistance barrier* for an HCV

205 DAA depends on many factors, and usually is defined as it relates to other drugs that are
206 approved or in development (Kwong, Najera, et al. 2011).[8]
207
208 Resistance studies should include evaluation of the potential for cross-resistance with approved
209 drugs, particularly focusing on those in the same drug class and other classes with the same viral
210 target. If a sponsor intends to develop a drug to be used in patients previously treated with drugs
211 in the same class, the activity of the investigational drug should be evaluated against HCV
212 variants that emerge in patients treated with other drugs in the class. In addition, the activity of
213 other representative approved drugs in the class should be evaluated against HCV variants
214 associated with resistance to the investigational drug.
215
216   *2.   General Considerations for Phase 1 and Phase 2 Development*
217
218 Early clinical evaluation of HCV DAAs should follow a rational approach to provide sufficient
219 data to establish safety, antiviral activity, and antiviral efficacy to support phase 3 trials. In
220 general, phase 1 trials should be conducted to assess safety, pharmacokinetics, and initial
221 antiviral activity of the DAA. Phase 2 trials should characterize the optimal dose and treatment
222 duration of the DAA(s) as part of combination regimens with regard to both antiviral activity and
223 safety.
224
225 Based on HCV replication dynamics in infected patients (Rong, Dehari, et al. 2010), the error-
226 prone nature of HCV genome replication, and the fact that the activity of a DAA is often reduced
227 by a single amino acid substitution in the drug target, multiple anti-HCV drugs with non-
228 overlapping resistance pathways generally are needed to suppress preexisting and emerging
229 drug-resistant variants for most patients to achieve SVR. Sponsors can choose to develop a
230 DAA for dosing in combination with other DAAs, and/or in regimens that include RBV. The
231 overall design of a phase 2 clinical development program should attempt to demonstrate the
232 contribution of individual drugs in the regimen (as described in section III.A.4., Efficacy
233 Considerations).
234
235 The following information is recommended to support phase 2 trials of multiple DAAs:
236
237 • Mechanism of action for each drug in the combination
238
239 • Resistance and cross-resistance patterns for each drug in the combination
240
241 • Combination antiviral activity data from cell culture studies
242
243 • Anti-HCV activity data from clinical trials (e.g., short-term monotherapy trials, or dose-
244 finding trials in combination with other antiviral drugs)
245
246 • Phase 1 human safety data on each drug
247

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

248   •   Dose selection rationale that considers potential for overlapping toxicities with the
249   individual components
250
251   •   Drug-drug interaction data if the metabolism profiles suggest an interaction potential
252   between drugs in the combination regimen
253
254 A primary objective of a phase 2 program should be demonstration of proof of concept of
255 efficacy (i.e., SVR) for DAA-containing regimens that are planned for study in phase 3. Early
256 on-treatment virologic responses and end-of-treatment responses often are not predictive of
257 SVR12 for DAA-containing regimens. Therefore, off-treatment responses such as SVR at post-
258 treatment weeks 4 and 12 (SVR4 and SVR12, respectively) should be available before
259 progression to phase 3. Specifically, for an end-of-phase 2 meeting, SVR4 data from all enrolled
260 patients in key supporting phase 2 trials, and all available SVR12 (or longer) data from phase 2
261 trials should be submitted to support progression to phase 3. All available SVR data from all
262 regimens under study in the drug development program should be used to select appropriate drug
263 regimens and patient populations for study in phase 3.
264
265 Phase 2 studies should include a representative population of patients with chronic HCV
266 infection. These populations can include, but are not limited to, Blacks/African Americans,
267 Hispanics, prior peg-IFN/RBV treatment failures, prior DAA treatment failures and patients with
268 compensated cirrhosis. Inclusion of these groups in phase 2 will assist in sample size
269 calculations and estimations of expected SVR rates in phase 3.
270
271 The following recommendations and examples are provided for potential phase 1 and phase 2
272 trial designs for HCV DAAs based on the current state of the field.
273
274   a.   Phase 1a/first-in-human trials
275
276 In general, we recommend single- and/or multiple-ascending-dose trials in healthy adult patients
277 to assess safety and pharmacokinetics for the first-in-human trials. Single-dose and short-
278 duration multiple-dose pharmacokinetic (PK) trials (see below) also can be conducted in HCV-
279 infected patients.
280
281   b.   Phase 1b (proof-of-concept) trials
282
283 The first proof-of-concept antiviral activity trial in HCV-infected patients should be a repeat-
284 dose, randomized, dose-ranging, monotherapy trial with collection of intensive PK, safety, and
285 HCV RNA data. Doses selected for phase 1b should be predicted to provide plasma and/or liver
286 tissue drug exposures that exceed by several-fold the protein binding-adjusted, cell culture EC_{50}
287 value of the drug for the relevant HCV genotype/subtype. The doses evaluated also should take
288 into account any safety margins previously identified in animal toxicology studies and in any
289 trials conducted in healthy volunteers. We generally recommend initial antiviral activity phase
290 1b trials be conducted in patients with CHC who are naïve to previous anti-CHC therapy
291 (including the investigational drug), and who have minimal fibrosis and no significant
292 comorbidities. Following demonstration of safety and antiviral activity in treatment-naïve
293 patients, sponsors can plan additional trials in treatment-experienced patients, as appropriate.

294
295 The maximum recommended duration of DAA monotherapy for an initial phase 1b trial depends
296 on several factors, such as the drug's mechanism of action, pharmacokinetics, expected
297 resistance barrier, study population, and availability of other drugs within and outside of the drug
298 class. For example, for an NS3/4A protease inhibitor or NS5A inhibitor with a low resistance
299 barrier and overlapping resistance pathways with other drugs in the class, the recommended
300 maximum duration of monotherapy is approximately 3 days. In this example, monotherapy
301 exceeding 3 days is not recommended because previous data with these DAA classes indicate
302 resistant virus is rapidly selected during monotherapy, and prolonged selection of resistance may
303 reduce the efficacy of other treatments and limit future treatment options for study patients.
304
305 On the other hand, a dosing duration of 3 to 7 days may be justified for a DAA that represents a
306 novel DAA class, has a relatively higher predicted resistance barrier, or requires several days of
307 dosing before achieving steady state plasma concentrations. Additionally, multiple weeks of
308 monotherapy could be appropriate for a drug that does not specifically target intracellular HCV
309 replication, for which demonstration of an HCV RNA decline would require loss of infected
310 cells. All DAA monotherapy trial protocols should include justification for the proposed
311 duration of treatment. Additionally, monotherapy trials of a drug with an unusually long half-life
312 that could lead to resistance should include plans to minimize risk to patients.
313
314   c.   Phase 2 trials with combination DAA regimens
315
316 Specific phase 2 trial designs for all oral, combination DAA regimens can vary greatly
317 depending on the drug class(es), intended patient population(s), HCV genotype, currently
318 available treatment options, and emerging data from other HCV DAA development programs.
319 In general, phase 2 trial designs should be randomized comparisons of several different DAA
320 combinations (all investigational or approved plus investigational) at various doses and treatment
321 durations. The number of DAAs in a regimen depends on individual drug potency and estimated
322 resistance barriers as determined in earlier stages of drug development. RBV can be included in
323 some or all of the treatment arms depending on the DAAs, the HCV genotype/subtype and the
324 patient population being evaluated. SVR12 is the recommended primary endpoint. Patients
325 should be followed through week 24 post-treatment cessation to further confirm the reliability of
326 SVR12 as a marker of virologic success. Trial randomization should be stratified according to
327 genotype/subtype or other key baseline characteristics predicted to have a significant effect on
328 treatment outcome.
329
330 Initial trials should include frequent HCV RNA monitoring and both patient- and treatment arm-
331 specific stopping rules for poor virologic outcomes (e.g., virologic breakthrough or relapse).
332 When feasible, protocols should include opportunities for patients with virologic failure to
333 receive appropriate alternative therapeutic regimens that could consist of investigational and/or
334 approved drugs. Final SVR12 and SVR24 efficacy outcome data from patients who received
335 protocol-specified re-treatment (approved and/or investigational) should be collected and
336 reported in final trial reports or other relevant regulatory submissions, because these data could
337 be informative for future clinical trial design as well as for clinical practice.
338

339 We anticipate that the number of single- and multiple-class DAA treatment-experienced patients
340 will increase as more HCV DAAs are studied in clinical trials and used in practice. Sponsors are
341 encouraged to develop and evaluate new treatment regimens to address the treatment challenges
342 for this population. Patients who did not achieve SVR with a full therapeutic duration of a DAA
343 combination regimen may be particularly difficult to treat. Many of the host and viral factors
344 that contributed to treatment failure with the prior DAA combination regimen(s) will remain,
345 such as cirrhosis, advanced liver disease, poor immune clearance of HCV replication complexes
346 and infected cells, high baseline HCV RNA levels, suboptimal exposures, poor adherence, poor
347 tolerability, or drug resistance (i.e., enrichment of HCV viral populations that are resistant to one
348 or multiple HCV DAA classes).

350 Multiple rounds of DAA treatment failure may severely limit treatment options for patients;
351 therefore, initial trials in DAA-experienced patients should include regimens and treatment
352 durations that are predicted to provide patients with the best chance of achieving SVR. For
353 example, exploration of relatively short treatment durations should be considered only after
354 preliminary evidence of SVR has first been demonstrated for longer treatment durations. Also,
355 because of the number of promising DAA classes approved or in development that would be
356 appropriate to test in DAA-experienced populations, we strongly encourage cross-company
357 collaboration when needed to construct a scientifically justified regimen.

359 Because re-treatment regimens may need to be individualized based on many factors such as
360 prior DAA treatment history and drug resistance characteristics, we are not able to provide
361 detailed guidance on appropriate trial designs for all possible circumstances. The need for drug
362 resistance screening depends on the specific drug classes in the regimen, emerging data from
363 other trials in DAA-experienced populations, and the characteristics of the patient population,
364 including HCV DAA exposure history, peg-IFN/RBV treatment history, and eligibility for a
365 treatment regimen containing peg-IFN/RBV.

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

374   *3.   Drug Development Population*

376 Drug development programs should include as broad a population as appropriate for the
377 characteristics of the antiviral drug. However, a DAA may have differential activity against
378 different HCV genotypes or subtypes; therefore, development can be targeted to a specific
379 genotype (e.g., genotype 1 versus genotype 2 or 3) or development can be targeted to regimens
380 that are optimized for specific subtypes. We recommend including patients diagnosed with
381 compensated cirrhosis in phase 2 and phase 3 trials. Also, we encourage the study of
382 combinations of DAA HCV antivirals in patients with the greatest need for new drugs, such as
383 patients with bleeding disorders, transplant patients, patients with advanced CKD, patients with
384 decompensated cirrhosis, and patients who have previously failed DAA-based treatment.

385
386 Similarly, patients on opioid maintenance therapy should be studied after the potential for drug-
387 drug interactions between the investigational drug and medications used for opioid maintenance
388 therapy is understood. DAAs can be studied in combination with other DAAs, with or without
389 RBV in HIV-1/HCV co-infected patients as soon as appropriate based on the availability of data
390 to choose an appropriate dose and rule out or manage important drug-drug interactions (see
391 section III.B.5.a., HIV-1/HCV co-infected patients). Supportive data may be needed such as
392 hepatic impairment trials and drug-drug interaction trials (e.g., antiretrovirals for HIV,
393 immunosuppressants for transplant) before trials in the above-mentioned subgroups are
394 conducted to define safety and pharmacokinetics.
395
396 CHC is a disease that is present worldwide and clinical trials typically are conducted
397 internationally. However, trials should include adequate U.S. patient representation to ensure
398 applicability of trial results to the U.S. population. An adequate representation of males and
399 females, races, ages, and weights is recommended during drug development, especially in phase
400 3 trials. Because race (e.g., Black, Asian) and ethnicity (e.g., Latino) may affect response rates
401 to anti-HCV treatment, the ability to ensure sufficient diversity in clinical trial demographics to
402 conduct meaningful analyses of such groups is important (Hepburn, Hepburn, et al. 2004). In
403 addition, we encourage sponsors to include investigators and sites who have experience treating
404 CHC patients who use intravenous drugs so that the clinical trial data can reflect the spectrum of
405 patients who will use CHC treatments after approval. Sponsors should share with the FDA their
406 pretrial initiation work to ensure the sites selected have sufficient numbers of patients from these
407 populations (e.g., women, Black/African Americans, Hispanic/Latinos, patients with cirrhosis,
408 patients with bleeding disorders, and patients using intravenous drugs) to enroll in phase 2 and
409 phase 3 clinical trials.
410
411   *4.   Efficacy Considerations*
412
413 Dose- and duration-finding should be performed in phase 2 trials to select optimal dose(s) and
414 treatment duration(s) for further evaluation in phase 3 trials. See section III.B.6., Dose Selection,
415 for additional considerations. For more detailed guidance on phase 3 trial design issues, see
416 section III.B.1., Trial Design.
417
418 Efficacy should be established in key subpopulations, including patients:
419
420   •   With and without cirrhosis
421   •   With compensated and decompensated liver disease
422   •   With HCV genotypes (e.g., 1, 2, 3, 4, 5, and 6, depending on susceptibility)
423   •   Who are DAA-naïve and DAA-experienced
424
425 Sponsors can submit an NDA to gain approval of a drug in a single population. Such an
426 application should include at least two adequate and well-controlled trials conducted in the
427 proposed population intended for labeling. Alternatively, sponsors can choose to pursue an
428 indication for different populations. In this case, the NDA should contain at least one adequate
429 and well-controlled phase 3 trial in each patient population, with adequate supporting data from
430 phase 2 trials (see section III.B., Phase 3 Efficacy Trial Considerations).

431
432   Trial designs for combinations of investigational DAAs with or without RBV should include
433   provisions for demonstrating that each component of the combination therapy contributes to the
434   desired effect. Establishing the contribution of each component can be accomplished using
435   factorial designs or modified factorial designs; however, we acknowledge that factorial designs
436   in which patients are randomized to only one new DAA may not be appropriate because of
437   concerns of suboptimal efficacy and emergence of resistance. As an alternative to factorial
438   designs, sponsors can show a DAA's contribution toward efficacy of a multiple DAA
439   combination regimen using other types of data. Examples of data supporting contribution of
440   efficacy include but are not limited to the following:
441
442   •   Cell culture data showing that DAA combinations slow or prevent the emergence of
443   resistance compared to single drugs
444
445   •   Early phase 2 clinical trial data showing that the addition of a drug to a DAA
446   combination improves SVR or reduces the emergence of viral variants with resistance-
447   associated substitutions
448
449   •   Data demonstrating improved efficacy of a combination regimen relative to historical
450   results with one or more components of the combination regimen
451
452   Sponsors should consult 21 CFR 300.50 regarding combining drug products in a single dosage
453   form. Additional recommendations for codevelopment of two investigational drugs can be found
454   in the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use*
455   *in Combination.*
456
457   HCV treatment development plans may be eligible for consideration under 21 CFR part 312,
458   subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses. HCV
459   treatment drugs also may be eligible for fast track, breakthrough,[9] and priority review
460   designation if the specifics of the relevant criteria are met.[10,11]
461
462   *5.   Safety Considerations*
463
464   In general, we recommend that initial marketing applications for drugs intended to treat CHC in
465   patients without decompensated cirrhosis contain a safety database of approximately 1,000 to
466   1,500 patients exposed to the proposed dose and duration of treatment. However, if significant
467   safety signals emerge during drug development, the safety database may need to be increased or

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[9] See the FDA fact sheet for breakthrough therapies at
http://www.fda.gov/regulatoryinformation/legislation/significantamendmentstothefdcact/fdasia/ucm329491.htm.

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

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

468 specific safety studies may need to be conducted. Flexibility in the recommended safety
469 database may be considered for investigational drugs that demonstrate substantial improvement
470 in efficacy and safety compared to currently available therapeutic options.
471
472 Data from randomized, controlled, and comparative trials are recommended to assess the safety
473 of the investigational drug. Ideally, to obtain comparative safety data, an active comparator in a
474 phase 3, controlled trial should be an antiviral drug that is recommended for treatment of chronic
475 HCV infection by authoritative scientific bodies based on clinical evidence that also reflects
476 current practice.[12] In some cases, use of an immediate versus deferred trial design to obtain
477 comparative safety data may be appropriate (see section III.B., Phase 3 Efficacy Trial
478 Considerations).
479
480 **B.** **Phase 3 Efficacy Trial Considerations**
481
482 *1.* *Trial Design*
483
484 The benefit-risk profile of the investigational drug and the available approved treatment options
485 for the indicated population are important factors to determine an appropriate trial design. We
486 recommend that at least one of the pivotal efficacy trials is designed as a randomized trial with
487 an active-control arm. The active comparator in a phase 3, controlled trial should be an antiviral
488 drug that is recommended for treatment of chronic HCV infection by authoritative scientific
489 bodies based on clinical evidence that also reflects current practice[13] at the time of trial initiation.
490 A randomized, active-controlled design allows for a direct comparison of the safety and efficacy
491 of the study regimen to an FDA-approved, recommended treatment option. We recommend
492 sponsors discuss with the FDA regarding the choice of an active control and choice of study
493 population before trial initiation. Although randomized, controlled, comparative trials are
494 preferable, in some situations (e.g., when no IFN-free recommended treatment option exists for
495 the population under study), single-arm trials using a historical control may be appropriate. Trial
496 design considerations by type of regimen and intended population are discussed in more detail
497 below.
498
499 a. Treatment-naïve and non-DAA treatment-experienced populations
500
501 A randomized, active-controlled noninferiority (NI) or superiority trial design is preferred over a
502 single-arm design, and at least one of the pivotal trials should be designed as such. The active
503 comparator in a phase 3, controlled trial should be an antiviral drug that is recommended for
504 treatment of chronic HCV infection by authoritative scientific bodies based on clinical evidence
505 that also reflects current practice.[14] Sponsors considering an NI trial design should discuss in
506 advance their justification of the NI margin, trial designs, and the data analysis plans.
507

---

[12] See the HCV treatment guidelines provided by the American Association for the Study of Liver Diseases for the
current HCV treatment recommendations (http://www.hcvguidelines.org).

[13] Ibid.

[14] Ibid.

508 In addition to a randomized, active-controlled trial or in situations where a randomized, active-
509 controlled trial is not feasible, and a single-arm trial is under consideration, we recommend an
510 immediate versus deferred placebo-controlled trial design in patients who are not considered to
511 need immediate treatment. In this design, patients should be randomized to the DAA-based
512 regimen or placebo for the intended treatment duration. At the end of treatment, patients
513 randomized to the placebo arm can receive the DAA-based regimen. The purpose of the
514 deferred treatment design is to collect comparative safety data and the primary efficacy
515 comparison is to a historical reference of a recommended HCV treatment regimen at the time of
516 trial initiation rather than to compare virologic response between trial arms. It is expected that
517 no patient will respond virologically while receiving placebo. Sponsors should include sufficient
518 information in the protocol to support the historical control used. Sponsors should also make
519 adequate provisions in the trial to maintain the trial blind and should minimize the potential for
520 patients in the placebo arm to drop out.
521
522 As an alternative to an immediate versus delayed treatment design, a dose or treatment duration
523 comparison trial could also be used. Consistent with the immediate versus delayed treatment
524 design, the primary efficacy comparison should be between each of the trial arms and a historical
525 reference of a recommended HCV treatment regimen at the time of trial initiation.
526
527   b.   DAA treatment-experienced population
528
529 Patients failing DAA-containing regimens constitute an emerging population in need of effective
530 HCV therapies. Because of the limited available efficacy data in this population, detailed
531 guidance for phase 3 trial design cannot be provided at this time. Sponsors should engage in
532 early discussions with the DAVP regarding development plans in prior DAA treatment-
533 experienced patients. In general, we anticipate phase 3 trials will be based on phase 2 proof-of-
534 concept efficacy data. Trial designs and the number of patients needed to support an indication
535 in patients who have failed treatment with DAA-containing regimens depend on the specific
536 characteristics of the patient population and the availability of other treatment regimens.
537
538   *2.   Trial Population*
539
540 Sponsors should ensure that patients enrolled in a trial have CHC as confirmed by one of the
541 following:
542
543 •   They are positive for anti-HCV antibody, HCV RNA, or an HCV genotype at least 6
544   months before screening, and positive for HCV RNA and anti-HCV antibody at the time
545   of screening
546
547   or
548
549 •   They are positive for anti-HCV antibody and HCV RNA at the time of screening with a
550   liver biopsy consistent with chronic HCV infection (or a liver biopsy performed before
551   enrollment with evidence of CHC disease, such as the presence of fibrosis)
552

553   *3.*   *Entry Criteria*

554

555   a.   Assessment of cirrhosis

556

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

563

564 To define presence or absence of cirrhosis, the use of a noninvasive modality in a protocol
565 should be supported by references that summarize performance characteristics and sensitivity
566 and specificity of the modality for identifying patients with cirrhosis.

567

568   b.   HCV genotype considerations

569

570 Certain DAAs demonstrate antiviral activity against multiple HCV genotypes, and sponsors may
571 wish to seek an indication for HCV treatment in several genotypes. Efficacy should be
572 established for each HCV genotype independently, and as seen with HCV genotype 1, some
573 DAA regimens may provide different efficacy for different subtypes. Enrollment of enough
574 patients with genotypes 4, 5, or 6 into trials to fully characterize efficacy for all the major
575 subtypes may not be feasible for trials conducted only in the United States because of the low
576 prevalence of these genotypes in the United States. Clinical trial data should be sufficient to
577 inform differences in response between each of the most common subtypes and identify whether
578 any subtypes have decreased efficacy to the proposed regimens. The total population size for
579 each genotype/subtype should be discussed with the DAVP before phase 3 trial initiation. The
580 nonclinical virology data should characterize the anti-HCV activity and resistance barrier of the
581 individual DAA(s) for HCV replicons (or other appropriate cell culture system) derived from
582 patient isolates from the major subtypes represented in the United States. See also section
583 III.C.3., Clinical Virology Considerations, for recommendations regarding HCV
584 genotype/subtype determination in clinical trials.

585

586   c.   DAA treatment experience

587

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

598

599   *4.   Randomization, Stratification, and Blinding*
600
601   We encourage sponsors to conduct double-blinded trials whenever feasible. The primary
602   endpoint (SVR12) is an objective endpoint; however, other aspects of the trial can be influenced
603   by knowledge of treatment assignment. In open-label protocols, patients may be more likely to
604   drop out of the trial if they know they are not receiving the new treatment, or investigators could
605   provide different levels of encouragement to continue.
606
607   Sponsors can consider stratification of patients by important baseline factors that are predictive
608   of SVR. The ideal stratification factors depend on the regimen and population studied, but could
609   include one or more of the following: HCV genotype/subtype, key baseline viral polymorphisms
610   or resistance-associated substitutions, prior treatment history, baseline HCV RNA, or
611   presence/absence of cirrhosis. In international trials, patients should be stratified by geographic
612   area (U.S. versus non-U.S.).
613
614   *5.   Specific Populations*
615
616   Patients with hepatic impairment or pre- or post-transplant patients, patients with advanced
617   CKD, and patients with decompensated cirrhosis are populations with unmet medical needs. We
618   strongly encourage sponsors to discuss early in development the process to determine
619   appropriate timing for initiating trials in these populations. This section also includes
620   information on HIV-1/HCV co-infected patients; although we no longer consider this population
621   as having an unmet medical need.
622
623   a.   HIV-1/HCV co-infected patients
624
625   Approximately 30 percent of patients infected with HIV-1 are co-infected with HCV (Sulkowski
626   2008). Patients with HIV-1/HCV co-infection are at higher risk of more rapid progression of
627   liver disease and higher rates of liver-related morbidity and mortality compared to HCV mono-
628   infected patients. The SVR rates in HIV-1/HCV co-infected patients receiving all oral antiviral
629   drugs are similar to HCV mono-infected patients. As a result, both HIV-1/HCV co-infected
630   patients and HCV mono-infected patients can enroll into the same clinical trial, and we strongly
631   encourage sponsors to have data on HIV-1/HCV co-infected patients at the time of submission of
632   an original NDA. See section III.B., Phase 3 Efficacy Trial Considerations.
633
634   HIV-1/HCV co-infected patients should be included in trials with HCV mono-infected patients
635   or in a separate trial to obtain efficacy and safety data at the proposed dose(s) and treatment
636   duration. The number of patients needed may depend on the effect of drug interactions on
637   exposures of the DAA. More patients may be needed if an increase or decrease in DAA is
638   expected because of drug interactions.
639
640   The NDA should also include the following data:
641
642   •   As needed, based on the investigational drug's potential for drug interactions, drug
643   interaction data with the most commonly used HIV drugs. The drug interaction data

644   should be available before trial initiation in HIV-1/HCV co-infected patients taking
645   antiretrovirals that are expected to have interactions with investigational DAA(s).
646
647   • Safety data including HIV RNA data to assess loss of HIV efficacy (rebound in HIV
648   RNA viral load) and changes in CD4 cell counts.
649
650   b.   Patients with decompensated cirrhosis and pre- or post-transplants
651
652   IFN-based regimens are not considered safe for patients with decompensated cirrhosis and may
653   be difficult to administer postliver transplant. As compared to compensated disease, treatment
654   with multiple investigational DAAs, with more drugs or for longer durations, may be needed to
655   achieve viral suppression.
656
657   We encourage active-controlled trials when feasible. However, safety and efficacy data can be
658   derived from dose or treatment duration comparison or single-arm, historical control trials. The
659   number of decompensated patients needed to support labeling claims should be discussed in
660   advance with the DAVP. The minimum acceptable safety database for this population will be
661   determined by the demonstrated safety profile of the regimen in other populations. As needed,
662   and based on a particular investigational drug's metabolic profile, sponsors should conduct drug
663   interaction trials with the most commonly used immunosuppressive drugs. These data should be
664   available before trials in post-transplant patients are initiated to support concomitant dosing of a
665   DAA regimen and immunosuppressive drugs.
666
667   We strongly recommend that an original NDA submission for the treatment of HCV with a
668   combination of DAAs contain some clinical data from patients with decompensated cirrhosis, as
669   well as pre- and post-transplant patients. Such data should include:
670
671   • As relevant, based on the investigational drug's potential for drug interactions, drug
672   interaction data with the most commonly used immunosuppressive drugs
673
674   • Safety data from a cohort or cohorts of patients with decompensated cirrhosis and pre- or
675   post-transplant recipients who received the drug for the recommended treatment duration
676
677   The safety evaluation of populations with advanced liver disease may need to incorporate
678   additional safety analyses to assess the safety of the investigational drug in this unique
679   population. Specific hepatic safety monitoring and treatment discontinuation criteria should be
680   discussed with the DAVP during the protocol development phase to incorporate case selection
681   criteria and laboratory cut-off values specific to the population.
682
683   Evaluation by an independent adjudication committee is encouraged to identify adverse events of
684   interest in this cohort of patients with decompensated liver disease and/or those listed for liver
685   transplantation. The NDA should include assessments based on the Model for End Stage Liver
686   Disease (MELD) and Child Pugh Turcotte (CPT) scores at 12-week post-treatment (SVR12 time
687   point) compared to the patient's baseline values.
688

689 Plans for expanded access trials or safety trials also should be considered for this population
690 early in development.
691
692   c.   Pediatric populations
693
694 The rapid evolution of HCV drug development and treatment affects pediatric development
695 programs. Therefore, we encourage sponsors to begin discussions about their pediatric
696 formulation and clinical development plan early in development because pediatric assessments
697 are required under the Pediatric Research Equity Act (PREA) as part of the overall drug
698 development program for a "new active ingredient, new indication, new dosage form, new
699 dosing regimen, or new route of administration,"[15] unless those assessments are waived or
700 deferred.[16] Sponsors are required to submit pediatric study plans — which would include an
701 outline of the pediatric assessments that the sponsor plans to conduct, or a request for a waiver or
702 deferral of the requirement to submit those assessments — no later than 60 days after an end-of-
703 phase 2 meeting or such other time as may be agreed upon by the FDA and the sponsor.[17] In the
704 absence of a serious safety signal in adults, we recommend sponsors enroll adolescents
705 concurrently with adults in phase 3 trials and make every effort to submit confirmatory PK and
706 safety data from a small cohort in this age group at the time of the original NDA. Note that,
707 because young children with HCV infection rarely have progressive liver disease requiring
708 treatment, evaluation of patients younger than 3 years of age may not be required.[18]
709
710 In addition to requiring pediatric assessments of certain drugs, PREA also requires that those
711 assessments be conducted using a formulation of the drug that is appropriate for each age group
712 being studied.[19] Formulation development is expected to be the most challenging aspect of
713 pediatric DAA development because many drug products will contain two or more drugs in a
714 fixed-dose combination. Adult formulations generally will be considered to be appropriate for
715 adolescent patients (approximately 12 to 18 years of age) (Momper, Mulugeta, et al. 2013), but
716 younger children, some of whom many not be able to swallow pills, may require different
717 formulations. Therefore, pediatric formulation development should begin as early as possible to
718 enable the creation of appropriate pediatric formulations of HCV drugs.
719
720 In general, pediatric clinical trials can be initiated after phase 2 adult data characterizing the
721 safety profile and preliminary evidence of efficacy (SVR) are available. Initial pediatric PK data

---

[15] See section 505B(a)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355c(a)(1).

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

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

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

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

722 and results of available modeling and simulation should be discussed with DAVP before dose
723 selection for pediatric treatment trials. Pediatric extrapolation of efficacy is acceptable for HCV
724 drugs because the course of HCV infection and the effects of DAAs are sufficiently similar
725 between adult and pediatric populations. Therefore, after critical PK parameters for a drug are
726 identified from adult data, pediatric development programs can rely on matching the relevant
727 pediatric and adult exposure parameters to demonstrate effectiveness in pediatric populations.
728 Additional data should be submitted to support safety in pediatric populations and to assess
729 whether SVR rates are comparable to those observed in adult trials.
730
731 Because the number of pediatric patients available for enrolling in HCV clinical trials may be
732 limited, we recommend that sponsors focus pediatric development on their *best available*
733 regimen that is expected to be highly effective based on adult data. We encourage sponsors to
734 work collaboratively to identify such regimens. In general, pediatric trials should provide
735 confirmatory PK data and a safety database of about 100 patients receiving the proposed dose for
736 the proposed duration of treatment and adequately distributed across the age range groups for
737 which studies are required and not waived or deferred. If clinical trials in adults have
738 demonstrated differences in safety profile or treatment regimen based on fibrosis stage, pediatric
739 patients should be assessed for presence or absence of cirrhosis using the most appropriate
740 modality for each study location. If biopsies are performed because they are clinically indicated,
741 biopsy data should be provided at the time of submission.
742
743   d.   Patients with advanced chronic kidney disease
744
745 HCV infection is a common comorbidity in hemodialysis patients. The prevalence rate of HCV
746 among patients undergoing hemodialysis within a U.S. hemodialysis network was reported as 7.8
747 percent (range: 5.5 to 9.8 percent) (Finelli, Miller, et al. 2005), and it is estimated that over
748 60,000 HCV-infected patients will require hemodialysis by 2020 (Butt, Wang, et al. 2011). A
749 significant relationship has been observed between HCV infection and increased mortality
750 among patients on long-term dialysis (Fabrizi, Dixit, et al. 2012).
751
752 HCV infection can also negatively affect renal transplantation. Compared to non-HCV-infected
753 CKD Stage 4/5 patients, HCV-infected CKD Stage 4/5 patients have poor graft survival and
754 higher overall mortality outcomes following renal transplantation (Fabrizi, Martin, et al. 2005;
755 Terrault and Adey 2007).
756
757 Peg-IFN-based regimens have been evaluated in advanced CKD patients, and dosing
758 recommendations are available for patients receiving dialysis. However, SVR rates are poor (56
759 percent), and tolerability is low (Fabrizi, Marti, et al. 2011). Therefore, the achievement of
760 optimal SVR rates in this population will likely require treatment with IFN- and RBV-free
761 combination DAA regimens.
762
763 We encourage active-controlled trials when feasible; however, at a minimum a delayed-
764 treatment, placebo-controlled group should be employed in clinical trials in this population. This
765 will facilitate interpretation of the safety data given the anticipated increased rate of adverse
766 events in the CKD population compared to those without CKD.
767

768 The minimum acceptable safety database for this population will be determined by the
769 demonstrated safety profile of the regimen in other populations. We encourage sponsors to study
770 an adequate number of patients in each of the important CKD subgroups (e.g., CKD Stage 4/5,
771 hemodialysis, and peritoneal dialysis). Trials should be stratified based on the degree of CKD
772 severity (and dialysis status) because drug clearance may be affected by these factors. We
773 encourage sponsors who are considering trials in this population to engage in early discussions
774 with the DAVP.
775
776   *6.   Dose Selection*
777
778 Results from proof-of-concept antiviral activity monotherapy trials can be used to guide dose
779 selection for subsequent phase 2 trials in which DAAs are studied for longer durations as part of
780 a combination regimen. We recommend that sponsors develop a mechanistic model of the
781 concentration-viral kinetics and the concentration safety using all available exposure, viral
782 kinetic, and safety data from previous studies to predict the most active and tolerable doses to be
783 evaluated in phase 2 trials. Such a model should include a mechanistically appropriate targeted
784 drug effect, components to describe virologic breakthrough, relapse, and long-term viral
785 response (i.e., SVR), and contain relevant covariates for describing differences in response
786 between HCV genotypes and subtypes or viral populations with or without drug resistance-
787 associated polymorphisms/substitutions. Results from patients infected with different HCV
788 genotypes and subtypes should be analyzed independently, as sample size permits, to begin to
789 evaluate dose-response relationships for relevant subpopulations. When applicable, these
790 mechanistic modeling approaches can use viral kinetic model structures and the corresponding
791 disease progression parameter values from the literature.
792
793 The model should be used to identify the appropriate population for treatment, and to reduce the
794 risk of selecting for resistant virus caused by subtherapeutic exposure. Optimal doses identified
795 based on single drug results may not be optimal for combination treatment, and the sponsor is
796 encouraged to evaluate a range of doses in subsequent trials.
797
798 To optimize the regimen with respect to dose and treatment duration in phase 3 trials, drug
799 efficacy data from phase 1 and phase 2 studies can be combined in a single model to predict SVR
800 in the planned trials. Such a model should be evaluated against on-treatment data of the regimen
801 and drug efficacy parameter estimates should be refined as necessary.
802
803   *7.   Efficacy Endpoints*
804
805 As mentioned, the recommended primary endpoint for approval in trials evaluating CHC
806 treatments is SVR12 (SVR at 12 weeks after completion of a scheduled course of therapy). Viral
807 RNA clearance (SVR12) should be measured using an FDA-approved sensitive and specific
808 quantitative HCV RNA assay. Use of unapproved assays should be discussed in advance with
809 the FDA.
810
811 Evaluating clinical outcomes in prospective, randomized controlled clinical trials of CHC is
812 challenging because of the difficulty of maintaining patients on a randomized arm without
813 intervening therapy for a sufficient duration (many years) to identify late-occurring clinical

814   events such as HCC or need for liver transplantation. However, multiple observational cohorts
815   show correlations between SVR24 and improvements in clinical outcomes such as development
816   of HCC, hepatic events, fibrosis, and all-cause mortality.[20] These observational data support the
817   use of SVR as a validated surrogate of HCV disease progression.
818
819   In a previous version of this guidance, SVR24 was the recommended endpoint for CHC clinical
820   trials. However, the FDA examined whether assessing SVR12 could be used as a primary
821   efficacy endpoint by examining the correlation between SVR12 and SVR24 in more than 13,000
822   patients pooled from multiple clinical trials of peg-IFN-based regimens (Chen, Florian, et al.
823   2013). In brief, there was a high rate of concordance between SVR12 and SVR24. Sensitivity
824   and specificity for SVR12 was 99 percent and 98 percent, respectively; therefore, SVR12 is
825   considered a suitable primary endpoint for registrational trials for both IFN-based and IFN-free
826   regimens. Subsequently, FDA reviews of clinical trials of IFN-free combination DAA regimens
827   have similarly demonstrated concordance of SVR12 and SVR24.
828
829   Although SVR12 has been shown to predict SVR24, the concordance of SVR12 and SVR24
830   results should continue to be assessed in clinical trials, particularly for new DAA classes and
831   combination drug regimens. At the time of NDA submission, all available SVR12 and SVR24
832   data from phase 2 and phase 3 trials should be analyzed to assess concordance of these results,
833   and the results of the analyses included in the application package. If the drug(s) is approved,
834   any additional emerging SVR24 data from phase 3 registrational trials generally will be
835   requested as a postmarketing commitment.
836
837   Secondary endpoints should include:
838
839   •   Virologic failure rate (relapse after end of treatment and virologic breakthrough on-
840   treatment) to aid in the optimization of a dosage regimen and treatment duration
841
842   •   SVR4 and SVR24 rates (i.e., virologic response at post-treatment week 4 or 24,
843   respectively)
844
845   •   End-of-treatment response rate
846
847   •   Rate of drug resistance emergence in patients who experience virologic failure
848
849   *8.*   *Trial Procedures and Timing of Assessments*
850
851   Recommended key time points for measuring HCV RNA depend on the drug regimen and
852   patient population. Key on-treatment measurements can include weeks 1, 2, 4, 8, 12, and 24, or
853   at the end of therapy. For all regimens, additional visits for HCV RNA monitoring should be
854   included as appropriate to ensure virologic breakthrough or other treatment futility is detected in
855   a timely manner.

---

[20] 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

856
857 Measurements of viral RNA at earlier time points can be used in protocol decision making for
858 determining appropriate futility rules for stopping treatment depending on an individual's
859 response.
860
861 After completion of treatment, viral RNA should be measured at weeks 4, 12, and 24 of follow-
862 up.
863
864   9.   *Statistical Considerations*
865
866   a.   Analysis populations
867
868 All patients who are randomized and receive at least one dose of assigned therapy during the trial
869 should be included in the primary efficacy analysis unless the FDA agrees in advance that certain
870 patients are not pertinent to the safety and effectiveness evaluation. However, if a substantial
871 proportion of randomized patients do not receive treatment in either or both arms then sensitivity
872 analyses also may be needed.
873
874   b.   Efficacy analyses
875
876 The primary efficacy analysis should be a comparison of the proportion of patients who achieve
877 SVR12 across trial treatment arms. This analysis determines whether effectiveness has been
878 demonstrated.[21]
879
880 For subgroup analyses, the analysis of SVR12 should be performed for patients with important
881 demographic and baseline characteristics (e.g., geographic region, sex, race, age group, HCV
882 genotype/subtype, HCV drug resistance-associated polymorphisms/substitutions, screening
883 serum HCV RNA, baseline weight, baseline body mass index, baseline alanine aminotransferase,
884 baseline fibrosis/cirrhosis, and, if applicable, prior response to DAA-based regimens).[22] The
885 purpose of these analyses is to evaluate the consistency of the SVR12 endpoint result across
886 these subgroups.
887
888 Single-arm trial designs where the SVR12 is compared to historical rates should prespecify the
889 historical rate in the protocol for efficacy comparisons. The historical rate should be based on
890 the intended regimen and patient population.
891
892 Effects on secondary endpoints are not sufficient to support efficacy in the absence of an effect
893 on the primary endpoint. The protocol should propose a multiple testing strategy for important
894 secondary endpoints that adjust for multiplicity to be applied after the result for the primary
895 endpoint is significant.

---

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

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

896
897 Patients who experience virologic relapse or who stop treatment because they did not adequately
898 suppress HCV RNA should be regarded as virologic failures in all analyses. For other patients
899 who discontinue treatment early, investigators should determine if these patients switched
900 treatments or added additional therapy. This information should be noted in the protocol case
901 report forms and captured in the electronic dataset. This information can be used to understand
902 reasons for discontinuation and how patients will be included in the analysis.
903
904   c. Noninferiority margin
905
906 In NI trials, the choice of an NI margin for statistical hypotheses should be discussed with the
907 DAVP before study initiation because one margin is not appropriate for all study designs. The
908 sponsor should justify a margin (M_1) based on prior knowledge of the quantitative contribution
909 of the active control (substituted part of the drug regimen) to the regimen as a whole. This
910 contribution should be determined in a similar population with a similar length of follow-up to
911 the proposed study. In addition, the NI margin (M_2) generally should be smaller than M_1 to
912 preserve a clinically important effect compared to an active control. If approved drugs have
913 response rates that are 95 percent or higher, a clinically acceptable NI margin (M_2) is 5 percent
914 or less; otherwise if the SVRs for approved drugs are all less than 95 percent, sponsors should
915 discuss the size of the NI margin with the DAVP. For NI testing, sponsors should employ two-
916 sided 95 percent confidence intervals adjusted for multiple comparisons or other appropriate
917 testing procedures.
918
919 Both NI and superiority can be assessed in an NI study provided that the NI comparison is
920 conducted first and superiority is conducted only after NI is met. For additional information
921 regarding NI studies in general, see ICH E10 and the draft guidance for industry *Non-Inferiority*
922 *Clinical Trials.*[23]
923
924   d. Handling of missing data
925
926 For the primary analysis, sponsors can consider a patient as having achieved SVR12 if the
927 patient's week 12 follow-up HCV RNA measurement is missing and the patient achieved
928 SVR24. Sponsors should consider a patient not to have achieved SVR12 if he or she
929 discontinues from a trial before having an HCV RNA measurement at 12 weeks of follow-up or
930 if the patient has missing HCV RNA values at the end of the scheduled 12- and 24-week follow-
931 up periods.
932
933 Sponsors should make every attempt to limit loss of patients from the trial. When the loss is
934 unavoidable, sponsors should explain the causes of missing data and attempt to determine the
935 final status of a patient who does not complete the protocol. Analyses excluding patients with
936 missing data or other post-treatment outcomes can be biased because patients who do not
937 complete the trial may differ substantially in both measured and unmeasured ways from patients
938 who remain in the trial.
939

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

940   Appropriate sensitivity analyses should be performed to demonstrate that the primary analysis is
941   robust to discontinuation and missing data. Sensitivity analyses can be performed using various
942   methods for imputing missing post-treatment virologic results at 12 weeks of follow-up.
943   Examples include but are not limited to using results from any available last post-treatment week
944   in place of the 12-week follow-up visit or treating a percentage of missing data as successes or
945   failures based on the overall results in which post-treatment data are available.
946

947   We recommend that sponsors collect detailed data on confirmation of reasons for discontinuation
948   (e.g., opportunity to enter another trial offering a promising new treatment, death or events
949   leading to death, disease progression, adverse events, loss to follow-up, withdrawal of consent,
950   noncompliance, pregnancy, protocol violations, not discontinued or not known to be
951   discontinued but data were missing at the final visit). The underlying reasons for discontinuation
952   should be interpreted. For example, the statistical analysis should include the number of patients
953   who withdrew consent or were lost to follow-up, or who discontinued because of adverse events.
954

955   e.   Interim analyses and data monitoring committees
956

957   If interim (or futility) analyses are performed, these analyses should be specified in the statistical
958   analysis plan (SAP). The purpose of the interim analysis should be stated in the SAP.
959

960   The SAP should include provisions that ensure the interim analysis does not compromise trial
961   integrity. Sponsors should refer to ICH E9 when considering the use of interim analyses in
962   clinical trials.
963

964   Sponsors should consider using a data monitoring committee for phase 3 trials evaluating
965   treatments for CHC, particularly if there are potential safety issues with one or more treatment
966   arms. A detailed charter with the composition of the committee members and the operational
967   details should be provided for review.[24]
968

969   f.   Statistical analysis plan
970

971   For any phase 2b trial (larger phase 2 trial intended to be supportive of efficacy for registration)
972   or phase 3 trial, we recommend sponsors provide a detailed SAP. The SAP can be either a
973   separate document or be within the protocol. The SAP should be submitted as soon as possible
974   after the protocol is finalized and before unblinding (when applicable) or conducting any
975   analysis. The SAP should have details on endpoint ordering, the analysis population, the
976   structure of statistical hypotheses to be tested, methods and statistical models of analyses
977   including the mathematical formulas, level of significance or alpha-level, and alpha adjustments
978   for multiple comparisons and interim analyses. Sponsors can modify an SAP as long as the trial
979   remains blinded, but sponsors should recognize that a detailed discussion with the DAVP may be
980   needed concerning data access and appropriate operating procedures for maintaining the integrity
981   of the blind.
982

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

983 The SAP should prospectively identify the covariates to be used in the analysis. Additionally,
984 the number of covariates should be kept to a minimum and limited to those that are expected to
985 strongly influence outcome.
986
987 Treatment-by-region and treatment-by-HCV genotype/subtype interaction should be investigated
988 and reported to assess consistency of the efficacy results. If multiple genotypes are included in a
989 single trial then efficacy analyses should be conducted separately within each genotype and there
990 should be enough patients to have sufficient power for the primary efficacy analysis within each
991 genotype.
992
993   *10.   Accelerated Approval (Subpart H) Considerations*
994
995 Accelerated approval, which can rely on a surrogate endpoint or an intermediate clinical
996 endpoint that is reasonably likely to predict clinical benefit,[25] does not apply to drug
997 development for hepatitis C because the endpoint used in clinical trials for full approval is
998 considered a validated surrogate endpoint (SVR12) that is known to predict clinical benefit.
999
1000   **C.   Other Considerations**
1001
1002   *1.   Relevant Nonclinical Safety Considerations*
1003
1004 Pharmacology/toxicology development for single HCV DAAs should follow existing guidances
1005 for drug development.[26]
1006
1007 The ICH guidance for industry referenced above, *M3(R2) Nonclinical Safety Studies for the*
1008 *Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*,
1009 recommends nonclinical combination studies to support clinical trials of combination drugs for
1010 entities in early stages of development. Section I.C., Scope of the Guidance, states,
1011 "Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g.,
1012 advanced cancer, resistant HIV infection, and congenital enzyme deficiency diseases) without
1013 current effective therapy also warrant a case-by-case approach to both the toxicological
1014 evaluation and clinical development in order to optimize and expedite drug development."
1015
1016 For new HCV drug combinations (consisting of two or more investigational drugs) that are not
1017 expected to represent an advantage (in terms of efficacy, tolerability, safety, use in specific
1018 populations or ease of administration) over approved combination therapies, combination
1019 toxicology studies usually should be submitted as part of an IND to conduct combination clinical
1020 trials. However, usually no more than two drugs should be tested simultaneously in a particular
1021 arm of a toxicology study. The design of such studies should be discussed with the DAVP. For
1022 DAA combinations that are expected to treat patients with limited or no treatment options or to
1023 improve response rates in patients at risk of serious morbidity or expected to be a substantial

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

[26] See the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.*

1024 improvement over approved therapies, the FDA may conclude that the benefits of these
1025 combinations outweigh the potential risks of foregoing the combination toxicology studies when
1026 all of the following apply:

1027

1028 • Mechanisms of action or in vitro data of potential off-target effects of the individual
1029 drugs do not suggest a potential for additive or synergistic toxicity of a serious nature.

1030

1031 • Studies in animals or humans of absorption, distribution, metabolism, and excretion of
1032 the individual drugs show no potential for an unmanageable interaction (one that cannot
1033 be addressed with dose adjustments) or serious toxicity for the combination.

1034

1035 • Toxicology studies (of at least 3 months duration) of the individual drugs show a
1036 substantial safety margin for the intended clinical dose(s) or exposures.

1037

1038 • Phase 1 clinical data in healthy volunteers or HCV-infected patients receiving the
1039 individual drugs show no substantial or unmanageable safety concerns. Phase 1 data
1040 should include single- and multiple-dose PK and safety trials, at minimum. Additional
1041 safety data from phase 1 and phase 2 trials are encouraged and may be needed if one or
1042 more of the drugs demonstrate a potential serious safety risk.

1043

1044 • There are no concerning overlapping toxicities for the individual drugs based on animal
1045 toxicology studies and phase 1 or phase 2 clinical data.

1046

1047 • Clinically significant PK-based drug interactions are considered unlikely or can be
1048 reliably managed with dose adjustments such that safety margins based on individual
1049 drug exposures are not exceeded.

1050

1051 After considering the above points, sponsors can first evaluate (in phase 1 and phase 2) drug
1052 combinations in HCV-infected patients who are treatment-naïve or have remaining treatment
1053 options. After initial trials in treatment-naïve patients (or in patients who have remaining
1054 approved treatment options) have helped to define the most active doses, patients with few or no
1055 remaining options can be studied. This approach helps to ensure that patients with no remaining
1056 treatment options are not exposed to suboptimal doses or combinations that could severely
1057 jeopardize their chance for achieving SVR.

1058

1059 Combination trials in healthy volunteers or patients with early stage CHC should not be the first-
1060 in-human trials unless the drugs cannot be administered separately and unless combination
1061 toxicology studies have been completed. We recommend referring to ICH guidance (i.e., ICH
1062 M3(R2)) when designing such studies.

1063

1064 Nonclinical combination studies of an investigational DAA plus an approved DAA, IFN, or
1065 RBV generally are not needed. Therefore, unless data from nonclinical studies of an
1066 investigational DAA suggest a potential for serious synergistic toxicity with an approved
1067 therapeutic drug, combination toxicology studies are not anticipated.

1068

1069 Applicants can choose to submit carcinogenicity studies with an initial NDA. Applicants who do
1070 not choose to do so may be required to submit carcinogenicity studies as postmarketing studies
1071 under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.[27] It is generally accepted
1072 that applicants who have clinical indications for HCV DAAs that have a treatment duration for
1073 24 or more weeks should conduct carcinogenicity studies.
1074
1075   2.   *Pharmacokinetic/Pharmacodynamic Considerations*
1076
1077   a.   Pharmacokinetic/Pharmacodynamic assessments
1078
1079 Trials conducted in HCV-infected patients should include assessment of pharmacokinetics and
1080 the relationship between drug exposure (e.g., C_{min}, C_{max}, or area under curve) and virologic
1081 success and toxicity in all patients.
1082
1083 Sponsors can use a combination of intensive and sparse sampling throughout development to
1084 characterize the pharmacokinetics of the investigational drug. For example, an intensive
1085 sampling schedule should be implemented in early phase monotherapy trials. In longer term
1086 trials, however, an intensive sampling schedule might not be feasible. Alternatively, sparse
1087 sampling from these trials can be combined with intensive PK data from earlier trials for
1088 analysis. Sparse PK samples should be obtained at the time of key virologic assessments, such
1089 as weeks 4, 12, and 24. Earlier PK sampling may be needed in cases where key virologic
1090 assessments occur earlier during treatment (e.g., week 1 or week 2). These data can then be
1091 subjected to appropriate population PK analysis. It is important to document dosing times and
1092 plasma sampling times.
1093
1094 Sponsors can use the following two broad approaches to characterize the relationship between
1095 exposure and viral kinetics or virologic success of the investigational drug, depending on the
1096 development stage and purpose of the analysis. Both approaches should account for differences
1097 in response between relevant viral subtypes and allow for exploration of relevant covariates.
1098 These analyses should consider virologic relapse and the development of resistance to the
1099 investigational drug when assessing differences between treatment regimens. When applicable,
1100 the developed exposure-response relationships should be used to support proposed dosing and
1101 treatment duration for subsequent trials.
1102
1103 • To aid the design of phase 2b and phase 3 trials, with respect to dose, duration, regimen
1104   choice, and population, a mechanistic approach relating drug concentrations and viral
1105   kinetics is most appropriate
1106
1107 • When sufficient SVR12 data are available, a simplified analysis relating the proportion of
1108   patients with virologic success and the appropriate exposure variable (e.g., C_{min} or area
1109   under curve) can be used to support evidence of effectiveness and justify dose selection
1110
1111 Exposure-response safety analyses should consider the common adverse events, toxicities that
1112 are unique to the investigational drug, and infrequent but severe events to determine whether the

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

1113   drug is safe. The appropriate exposure parameter and modeling approach depends on the
1114   investigational drug and toxicity.
1115
1116   b.   Specific pharmacokinetic evaluation
1117
1118   We strongly encourage PK evaluation in patients with renal impairment and hepatic impairment,
1119   to inform the need for dose modifications, early in drug development so these patients can be
1120   enrolled into phase 2 and phase 3 trials as appropriate. In general, it is recommended that these
1121   studies be conducted with the final regimen rather than the individual components separately.
1122   Specific recommendations related to trial design and data analysis can be found in the relevant
1123   FDA clinical pharmacology guidances.
1124
1125   3.   *Clinical Virology Considerations*
1126
1127   a.   HCV RNA assessments and data reporting
1128
1129   For antiviral activity and efficacy trials, HCV RNA levels should be measured using a sensitive
1130   and specific quantitative assay. Clinical trial protocols should describe the HCV RNA assay(s)
1131   to be used, including a brief description of assay performance characteristics. Protocols or study
1132   reports should include the names and addresses of the laboratories conducting HCV RNA
1133   assessments (e.g., central laboratory or assay vendor).
1134
1135   For clinical trial protocols, study reports, and HCV RNA datasets, clear and consistent language
1136   should be used to describe low-level HCV RNA results, following guidelines for reporting HCV
1137   RNA levels as described in FDA-approved assay package inserts. Specifically, HCV RNA
1138   levels that are detected but less than lower limit of quantitation (LLOQ) should be reported as
1139   "< {LLOQ value in IU/mL} Detected," and HCV RNA levels that are not detected should be
1140   reported as "Target Not Detected" or "HCV RNA Not Detected." Use of terms such as
1141   *undetectable* or greater than or less than the limit of detection (LOD) ("> LOD" or "< LOD,"
1142   respectively) is not recommended, even if the validated assay LOD and LLOQ are equal,
1143   because HCV RNA levels less than LOD can still be detected at a certain rate depending on the
1144   actual HCV RNA concentration.
1145
1146   A detected/not detected HCV RNA cutoff can be problematic for study endpoints or treatment
1147   decision making because it is inherently less reproducible compared to an HCV RNA cutoff that
1148   is within the validated quantitative range of the assay. Therefore, sponsors are encouraged to use
1149   the assay LLOQ (or other quantitative HCV RNA threshold as appropriate) as the HCV RNA
1150   cutoff for treatment futility rules and study endpoints including SVR, virologic relapse, and
1151   virologic breakthrough. See also Appendix A for recommended terms and definitions related to
1152   virologic response and treatment history.
1153
1154   b.   HCV genotype/subtype determination
1155
1156   A validated assay with accuracy that is comparable to HCV genotyping/subtyping reference
1157   methods (Smith, Bukh, et al. 2014) should be used for HCV genotype or subtype screening and
1158   randomization of patients; use of an FDA-approved assay is recommended. Clinical trial

1159   protocols should describe the HCV genotype/subtype assay(s) to be used, including a brief
1160   description of assay performance characteristics. Genotyping/subtyping assays (or historical
1161   data) based only on nucleotide sequence analysis of the 5'-noncoding region of the HCV genome
1162   should be avoided because of poor performance in distinguishing between certain HCV
1163   genotypes and subtypes 1a and 1b (Chevaliez, Bouvier-Alias, et al. 2009). Clinical assays used
1164   for HCV genotype/subtype determination may not resolve HCV subtypes other than 1a and 1b.
1165   Therefore, for patients with nongenotype 1 HCV infection, retrospective analyses should be
1166   conducted to identify HCV subtypes based on reference methods (Smith, Bukh, et al. 2014) or
1167   phylogenetic analysis of the drug target sequence(s).
1168
1169   c.   Resistance analyses
1170
1171   For efficacy trials, treatment-emergent resistance testing should be performed for patients who
1172   do not achieve SVR. Treatment-emergent genotypic and phenotypic resistance analyses should
1173   focus on samples collected while patients are on the investigational drug; if on-treatment HCV
1174   RNA levels are not adequate for analysis, then the first available follow-up sample with adequate
1175   HCV RNA should be analyzed. Any changes, including mixtures, in the amino acid coding
1176   sequence of the targeted genome region present in on-treatment or follow-up samples, but not in
1177   the baseline sample, should be reported as having developed during therapy. Enrichment of
1178   substitutions from mixtures at baseline should also be reported; how these data are considered in
1179   treatment-emergent resistance analyses may depend on clinical trial design and nucleotide
1180   sequencing methods. Similar treatment-emergent resistance analyses should be conducted for all
1181   patients in early phase monotherapy trials.
1182
1183   Pretreatment samples from clinical trial patients should be analyzed to identify HCV genetic
1184   polymorphisms in DAA target genes, and the effect of HCV polymorphisms on treatment
1185   response should be evaluated. These analyses should consider both the investigational DAA(s)
1186   as well as any background DAA(s) evaluated in combination. The prevalence of HCV
1187   populations carrying detectable resistance-associated polymorphisms should be determined, both
1188   in the full study population and in U.S. study patients specifically.
1189
1190   Patients who have detectable resistance-associated substitutions at treatment cessation or follow-
1191   up should be followed for an extended period, at least 1 year after treatment cessation or until the
1192   initiation of alternative HCV therapies, to assess the persistence of resistance-associated
1193   substitutions. The potential persistence of resistance-associated substitutions should be
1194   characterized for patients enrolled in phase 1 and phase 2 clinical trials so that preliminary long-
1195   term follow-up data are obtained by the time of completion of phase 3 trials. Genotyping
1196   methodology should be capable of assessing the quantity of resistant viruses during the
1197   outgrowth of wild-type virus.
1198
1199   Clinical trials of DAA regimens for patients previously exposed to DAA(s) of the same class(es)
1200   or other classes with the same viral target should include plans to explore the efficacy effect of
1201   prior DAA exposure, considering the duration of prior DAA exposure, time since prior DAA
1202   exposure, and the detection of DAA resistance-associated substitutions. For initial proof-of-
1203   concept studies in these patient populations, sponsors are encouraged to use sensitive and
1204   quantitative genotypic resistance assays to characterize the relative and absolute quantity of

1205 DAA-resistant variants at baseline, and relate these findings to treatment outcome. Results from
1206 these analyses should be used to guide the design of subsequent trials; for example, whether
1207 inclusion should be based on the detection of DAA-resistant viral populations.
1208
1209 Drug resistance-associated polymorphisms or substitutions observed in clinical trials should be
1210 evaluated phenotypically by introducing the changes into the HCV genome, and determining the
1211 conferred fold-shift in susceptibility to the drug using appropriate cell culture or biochemical
1212 assays. Sponsors should perform phenotypic analyses of HCV replicons or viruses derived from
1213 treated patients if resistance is suspected but treatment-emergent genotypic resistance patterns
1214 are unclear. Fold-changes in antiviral activity should be reported based on EC_{50} and EC_{90} (or
1215 EC_{95}) values. Because resistance pathways can be complex, and a variety of factors can affect
1216 drug resistance in treated patients, the lack of an observed phenotypic reduction in HCV
1217 susceptibility conferred by a specific amino acid substitution does not necessarily preclude a role
1218 for the substitution in HCV drug resistance.
1219
1220 Because nucleotide sequencing technologies and data standards are evolving, sponsors should
1221 consult with the DAVP for current recommendations regarding the organization and submission
1222 of drug resistance datasets.
1223
1224   *4.   Expanded Access Considerations*
1225
1226 Some HCV-infected patients who are unable to take or who have not responded to approved
1227 treatments and who are at substantial risk of liver disease progression may be able to seek
1228 treatment with an investigational drug or drugs, before the drug(s) is approved, through
1229 expanded access under 21 CFR 312.310, 312.315, or 312.320. Treatment INDs or treatment
1230 protocols for DAAs may be appropriate when sufficient clinical trial data have been generated to
1231 develop a treatment protocol (including planned dosing) that meets the requirements of 21 CFR
1232 312.320. Ideally, submission of a treatment IND or protocol should occur after phase 3 trials are
1233 fully enrolled or well underway so as to avoid interference with phase 3 drug development. A
1234 treatment IND or protocol can provide access to an investigational drug while phase 3 trials are
1235 being completed, analyzed, submitted, and reviewed by the FDA. Alternatively, individual
1236 patient and intermediate-size patient population expanded access may be possible. In contrast to
1237 treatment INDs/protocols for larger populations during or after phase 3 trials, expanded access
1238 for individual patient and intermediate size patient populations can occur earlier in drug
1239 development.
1240
1241 Historically, expanded access programs for the treatment of HIV infection allowed many patients
1242 to gain access to lifesaving drugs. However, for some individuals, expanded access to an
1243 investigational drug resulted in what amounted to sequential monotherapy and the emergence of
1244 multidrug resistance. Because treatment of CHC requires multiple drugs to achieve SVR and to
1245 reduce the emergence of drug resistance to single drugs or drug classes, expanded access
1246 programs that include two or more investigational drugs or that allow co-enrollment in several
1247 expanded access programs simultaneously are desirable, particularly for difficult-to-treat
1248 populations. However, treatment use through expanded access of multiple investigational drugs
1249 should be supported by:
1250

1251   •   Data and rationale that characterize the potential for PK-based drug interactions and
1252   potential for overlapping toxicity; data to support dose modifications if needed
1253
1254   •   Information suggesting the potential for additive or synergistic activity and no or minimal
1255   overlapping resistance profiles
1256
1257 See section III.A.2., General Considerations for Phase 1 and Phase 2 Development, for the data
1258 needed to support treatment use through expanded access of multiple investigational drugs in a
1259 treatment regimen.
1260

1261 **GLOSSARY OF ACRONYMS**
1262

1263	CC	cytotoxic concentration
1264	CHC	chronic hepatitis C
1265	CKD	chronic kidney disease
1266	DAA	direct-acting antiviral
1267	DNA	deoxyribonucleic acid
1268	EC	effective concentration
1269	HCC	hepatocellular carcinoma
1270	HCV	hepatitis C virus
1271	HCV RNA	hepatitis C virus ribonucleic acid
1272	HIV	human immunodeficiency virus
1273	IFN	interferon
1274	IU	international unit
1275	LLOQ	lower limit of quantitation
1276	LOD	limit of detection
1277	mL	milliliter
1278	NI	noninferiority
1279	Peg	pegylated
1280	PK	pharmacokinetic
1281	RBV	ribavirin
1282	RNA	ribonucleic acid
1283	SAP	statistical analysis plan
1284	SVR	sustained virologic response
1285	SVR4	sustained virologic response 4 weeks after stopping treatment
1286	SVR12	sustained virologic response 12 weeks after stopping treatment
1287	SVR24	sustained virologic response 24 weeks after stopping treatment

1288

REFERENCES

1291 Afdhal, N, KR Reddy, DR Nelson, E Lawitz, SC Gordon, E Schiff, R Nahass, R Ghalib, N
1292 Gitlin, R Herring, J Lalezari, ZH Younes, PJ Pockros, AM Di Bisceglie, S Arora, GM
1293 Subramanian, Y Zhu, H Dvory-Sobol, JC Yang, PS Pang, WT Symonds, JG McHutchison, AJ
1294 Muir, M Sulkowski, and P Kwo, 2014, Ledipasvir and Sofosbuvir for Previously Treated HCV
1295 Genotype 1 Infection, N Engl J Med, April 17;370(16):1483-93.

1297 Arase, Y, K Ikeda, F Suzuki, Y Suzuki, S Saitoh, M Kobayashi, N Akuta, T Someya, R Koyama,
1298 T Hosaka, H Sezaki, M Kobayashi, and H Kumada, 2007, Long-Term Outcome After Interferon
1299 Therapy in Elderly Patients With Chronic Hepatitis C, Intervirology, 50(1):16-23.

1301 Armstrong, GL, A Wasley, EP Simard, GM McQuillan, WL Kuhnert, and MJ Alter, 2006, The
1302 Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002, Ann Intern
1303 Med., May 16;144(10):705-14.

1305 Arnold, JJ, SD Sharma, JY Feng, AS Ray, ED Smidansky, ML Kireeva, A Cho, J Perry, JE Vela,
1306 Y Park, Y Xu, Y Tian, D Babusis, O Barauskas, BR Peterson, A Gnatt, M Kashlev, W Zhong,
1307 and CE Cameron, 2012, Sensitivity of Mitochondrial Transcription and Resistance of RNA
1308 Polymerase II Dependent Nuclear Transcription to Antiviral Ribonucleosides, PLoS Pathog,
1309 8(11):e1003030.

1311 Backus, LI, D Boothroyd, B Phillips, P Belperio, J Halloran, and L Mole, 2011, A Sustained
1312 Virologic Response Reduces Risk of All-Cause Mortality in Patients With Hepatitis C, Clin
1313 Gastroenterol Hepatol, June 9;(6):509-516.

1315 Braks, RE, N Ganne-Carrie, H Fontaine, J Paries, V Grando-Lemaire, M Beaugrand, S Pol, and
1316 JC Trinchet, 2007, Effect of Sustained Virological Response on Long-Term Clinical Outcome in
1317 113 Patients With Compensated Hepatitis C-Related Cirrhosis Treated By Interferon Alpha and
1318 Ribavirin, World J Gastroenterol, Nov 14;13(42):5648-53.

1320 Bruno, S, T Stroffolini, M Colombo, S Bollani, L Benvegnù, G Mazzella, A Ascione, T
1321 Santantonio, F Piccinino, P Andreone, A Mangia, GB Gaeta, M Persico, S Fagiuoli, PL Almasio,
1322 and Italian Association of the Study of the Liver Disease, 2007, Sustained Virological Response
1323 to Interferon-Alpha Is Associated With Improved Outcome in HCV-Related Cirrhosis: A
1324 Retrospective Study, Hepatology, Mar;45(3):579-87.

1326 Butt, AA, X Wang, and LF Fried, 2011, HCV Infection and the Incidence of CKD, Am J Kidney
1327 Dis, 57(3):396-402.

1329 Casey, L and W Lee, 2013, Hepatitis C Virus Therapy Update 2012, Curr Opin Gastroenterol,
1330 May 29(3): 243-9.

1332 Chen, J, J Florian, W Carter, RD Fleischer, TS Hammerstrom, PR Jadhav, W Zeng, J Murray,
1333 and D Birnkrant, 2013, Earlier Sustained Virologic Response End Points for Regulatory

1334 Approval and Dose Selection of Hepatitis C Therapies, Gastroenterology, Mar (epub ahead of
1335 print).
1336
1337 Chevaliez, S, M Bouvier-Alias, R Brillet, and JM Pawlotsky, 2009, Hepatitis C Virus (HCV)
1338 Genotype 1 Subtype Identification in New HCV Drug Development and Future Clinical Practice,
1339 PLoS One, Dec 8;4(12):e8209.
1340
1341 Coelmont, L, J Paeshuyse, MP Windisch, E De Clercq, R Bartenschlager, and J Neyts, 2006,
1342 Ribavirin Antagonizes the In Vitro Anti-Hepatitis C Virus Activity of 2'-C-methylcytidine, the
1343 Active Component of Valopicitabine, Antimicrob Agents Chemother, Oct;50(10):3444-6.
1344
1345 Fabrizi, F, V Dixit, and P Messa, 2012, Impact of Hepatitis C on Survival in Dialysis Patients: A
1346 Link With Cardiovascular Mortality?, J Viral Hepat, 19:601-7.
1347
1348 Fabrizi, F, P Martin, V Dixit, S Bunnapradist, and G Dulai, 2005, Hepatitis C Virus Antibody
1349 Status and Survival After Renal Transplantation: Meta-Analysis of Observational Studies, Am J
1350 Transplant, 5:1452-61.
1351
1352 Fabrizi, F, P Martin, V Dixit, and P Messa, 2011, Combined Antiviral Therapy of Hepatitis C
1353 Virus in Dialysis Patients: Meta-Analysis of Clinical Trials, 2011, J Viral Hepatitis, 18:263-69.
1354
1355 Finelli, L, JT Miller, JI Tokars, MJ Alter, and MJ Arduino, 2005, National Surveillance of
1356 Dialysis-Associated Diseases in the United States, Seminars in Dialysis, 18(1):52-61.
1357
1358 Gane, EJ, 2008, The Natural History of Recurrent Hepatitis C and What Influences This, Liver
1359 Transpl., Suppl2: S36-44.
1360
1361 Ge, D, J Fellay, AJ Thompson, JS Simon, KV Shianna, TJ Urban, EL Heinzen, P Qiu, AH
1362 Bertelsen, AJ Muir, M Sulkowski, JG McHutchison, and DB Goldstein, 2009, Genetic Variation
1363 in IL28B Predicts Hepatitis C Treatment-Induced Viral Clearance, Nature, 461:399-401.
1364
1365 Gower, E, C Estes, S Blach, K Razavi-Shearer, and H Razavi, 2014, Global Epidemiology and
1366 Genotype Distribution of the Hepatitis C virus Infection, J. Hepatol., 61(1 Suppl):S45-57.
1367
1368 Harrington, PR, W Zeng, and LK Naeger, 2012, Clinical Relevance of Detectable but Not
1369 Quantifiable Hepatitis C Virus RNA during Boceprevir or Telaprevir Treatment, Hepatology,
1370 Apr;55(4):1048-57.
1371
1372 Hepburn, MJ, LM Hepburn, NS Cantu, MG Lapeer, and EJ Lawitz, 2004, Differences in
1373 Treatment Outcome for Hepatitis C Among Ethnic Groups, Am J Med, Aug 1;117(3):163-8.
1374
1375 Imai, Y, S Kawata, S Tamura, I Yabuuchi, S Noda, M Inada, Y Maeda, Y Shirai, T Fukuzaki,
1376 I Kaji, H Ishikawa, Y Matsuda, M Nishikawa, K Seki, and Y Matsuzawa, 1998, Relation of
1377 Interferon Therapy and Hepatocellular Carcinoma in Patients With Chronic Hepatitis C, Osaka
1378 Hepatocellular Carcinoma Prevention Study Group, Ann Intern Med, Jul 15;129(2):94-9, PMID:
1379 9669992.

1380
1381   Klevens, MR, J Dale, RJ Hu, and S Homberg, 2012, Evolving Epidemiology of Hepatitis C
1382   Virus in the United States, Clinical Infectious Diseases, 55(S1):S3-9.
1383
1384   Kwong, AD, I Najera, J Bechtel et al., 2011, Sequence and Phenotypic Analysis for Resistance
1385   Monitoring in Hepatitis C Virus Drug Development: Recommendations from the HCV DRAG,
1386   Gastroenterology, Mar;140(3):755-60.
1387
1388   Ly, KN, J Xing, RM Klevens, RB Jiles, JW Ward, and SD Holmberg, 2012, The Increasing
1389   Burden of Mortality from Viral Hepatitis in the United States Between 1999 and 2007, Ann
1390   Intern Med., Feb 21;156(4):271-8.
1391
1392   Manos, MM, WK Zhao, VA Shvachko, N Volkova, CP Quesenberry, Viral Hepatitis Registry,
1393   and Kaiser Permanente Division of Research, Oakland, CA, 2009, Long Term Outcomes in
1394   Patients Treated With Peg-Interferon/Ribavirin Therapy for Hepatitis C: The Substantial Effect
1395   of Sustained Viral Response (SVR) on Liver Disease, Mortality and Diabetes, 13th International
1396   Symposium on Viral Hepatitis and Liver Disease, Abstract PL-3.
1397
1398   Marroquin, LD, J Hynes, JA Dykens, JD Jamieson, and Y Will, 2007, Circumventing the
1399   Crabtree Effect: Replacing Media Glucose with Galactose Increases Susceptibility of HepG2
1400   Cells to Mitochondrial Toxicants, Toxicol. Sci, 97(2):539-47.
1401
1402   Momper, JD, Y Mulugeta, and DJ Green, 2013, Adolescent Dosing and Labeling Since the Food
1403   and Drug Administration Amendments Act of 2007, JAMA Pediatr., 167:926-932.
1404
1405   Okanoue, T, Y Itoh, M Minami, S Sakamoto, K Yasui, M Sakamoto, K Nishioji, Y Murakami,
1406   and K Kashima, 1999, Interferon Therapy Lowers the Rate of Progression to Hepatocellular
1407   Carcinoma in Chronic Hepatitis C but not Significantly in an Advanced Stage: A Retrospective
1408   Study in 1148 Patients, Viral Hepatitis Therapy Study Group, J Hepatol, Apr;30(4):653-9,
1409   PMID: 10207807.
1410
1411   Poordad, F, JP Bronowicki, SC Gordon, S Zeuzem, IM Jacobson, MS Sulkowski, T Poynard, TR
1412   Morgan, C Molony, LD Pedicone, HL Sings, MH Burroughs, V Sniukiene, N Boparai, VS
1413   Goteti, CA Brass, JK Albrecht, BR Bacon, and SPRINT-2 AND RESPOND-2 Investigators,
1414   2012, Factors that Predict Response of Patients with HCV Infection to Boceprevir,
1415   Gastroenterology, May 21 (Epub ahead of print).
1416
1417   Rong, L, H Dahari, RM Ribeiro, and AS Perelson, 2010, Rapid Emergence of Protease Inhibitor
1418   Resistance in Hepatitis C Virus, Science Translational Medicine, May 5;2(30):30ra32.
1419
1420   Shiratori, Y, Y Ito, O Yokosuka, F Imazeki, R Nakata, N Tanaka, Y Arakawa, E Hashimoto,
1421   K Hirota, H Yoshida, Y Ohashi, M Omata, and Tokyo-Chiba Hepatitis Research Group, 2005,
1422   Antiviral Therapy for Cirrhotic Hepatitis C: Association With Reduced Hepatocellular
1423   Carcinoma Development and Improved Survival, Ann Intern Med, Jan 18;142(2):105-14, PMID:
1424   15657158.
1425

1426 Simmons, B, J Saleem, K Heath, G Cooke, and A Hill, 2015, Long-Term Treatment Outcomes
1427 of Patients Infected with Hepatitis C Virus: A Systematic Review and Meta-Analysis of the
1428 Survival Benefit of Achieving a Sustained Virologic Response, CID, 61:730-740.
1429
1430 Singal, AG, M Volk, D Jensen, et al., 2010, A Sustained Viral Response Is Associated with
1431 Reduced Liver Related Morbidity and Mortality in Patients with Hepatitis C Virus, Clin
1432 Gastroenterol Hepatol, 8:280-288.
1433
1434 Smith, DB, J Bukh, C Kuiken, AS Muerhoff, CM Rice, JT Stapeleton, and P Simmonds, 2014,
1435 Expanded Classification of Hepatitis C Virus into 7 Genotypes and 67 Subtypes: Updated
1436 Criteria and Genotype Assignment Web Resource, Hepatology, 59(1):318-327.
1437
1438 Snoeck, E, P Chanu, M Lavielle, P Jacqmin, EN Jonsson, K Jorga, T Goggin, J Grippo, NL
1439 Jumbe, and N Frey, 2010, A Comprehensive Hepatitis C Viral Kinetic Model Explaining Cure,
1440 Clin Pharmacol Ther, Jun;87(6):706-13, Epub 2010 May 12.
1441
1442 Sulkowski, MS, 2008, Viral Hepatitis and HIV Coinfection, J Hepatol, Feb;48(2):353-67.
1443
1444 Terrault, NA and DB Adey, 2007, The Kidney Transplant Recipient With Hepatitis C Infection:
1445 Pre- and Posttransplantation Treatment, Clin J Soc Nephrol, 2:563-75.
1446
1447 Veldt, BJ, EJ Heathcote, H Wedemeyer, J Reichen, WP Hofmann, S Zeuzem, MP Manns, BE
1448 Hansen, SW Schalm, and HL Janssen, 2007, Sustained Virologic Response and Clinical
1449 Outcomes in Patients With Chronic Hepatitis C and Advanced Fibrosis, Ann Intern Med,
1450 147:677-684.
1451
1452 Yoshida, H, Y Arakawa, M Sata, S Nishiguchi, M Yano, S Fujiyama, G Yamada, O Yokosuka,
1453 Y Shiratori, and M Omata, 2002, Interferon Therapy Prolonged Life Expectancy Among Chronic
1454 Hepatitis C Patients, Gastroenterology, Aug;123(2):483-91.
1455
1456 Yoshida, H, Y Shiratori, M Moriyama et al., 1999, Interferon Therapy Reduces the Risk for
1457 Hepatocellular Carcinoma: National Surveillance Program of Cirrhotic and Noncirrhotic
1458 Patients With Chronic Hepatitis C in Japan, IHIT Study Group, Inhibition of
1459 Hepatocarcinogenesis by Interferon Therapy, Ann Intern Med, Aug 3;131(3):174-81.
1460
1461 Zeuzem, S, V Soriano, T Asselah, JP Bronowicki, AW Lohse, B Mullhaupt, M Schuchmann,
1462 M Bourliere, M Buti, S Roberts, E Gane, JO Stern, G Kukolj, L Dai, WO Bocher, and FJ Mensa,
1463 2012, SVR4 and SVR12 with an Interferon-Free Regimen of BI 201335 and BI 207127, +/-
1464 Ribavirin, in Treatment-Naïve Patients with Chronic Genotype-1 HCV Infection: Interim
1465 Results of SOUND-C2, EASL International Liver Congress, Abstract 101.
1466

1467 **APPENDIX A:**
1468 **STUDY POPULATION TERMS AND TREATMENT RESPONSE DEFINITIONS**
1469
1470 **Points to Consider**
1471
1472 Table A includes recommended terms and definitions for documentation of prior treatment
1473 history and responses (i.e., for trial inclusion criteria).
1474
1475 • Some flexibility in the definitions may be appropriate, particularly when the level of
1476   detail indicated in the table is not typically available.
1477
1478 • Peg-IFN refers to a pegylated interferon product.
1479
1480 • For prior treatment history, multiple terms can be considered as appropriate to document
1481   responses to multiple rounds of treatment. If only one term is used per patient, the most
1482   recent DAA-based treatment should take precedence.
1483
1484 • Specific details regarding all prior drug/class experience should be noted as part of
1485   protocol-specified data collection.
1486
1487 **Table A: Recommended Terms and Definitions for Treatment History**

TREATMENT-NAÏVE	Naïve to all anti-HCV treatment.
P/R-ONLY EXPERIENCED*	Did not achieve 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).

1488 * P/R = peg-IFN/RBV
1489

1490   Table B includes recommendations for protocol definitions of response/nonresponse to
1491   investigational regimens.
1492
1493   **Table B: Recommended Protocol Definitions for Response/Nonresponse**

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

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