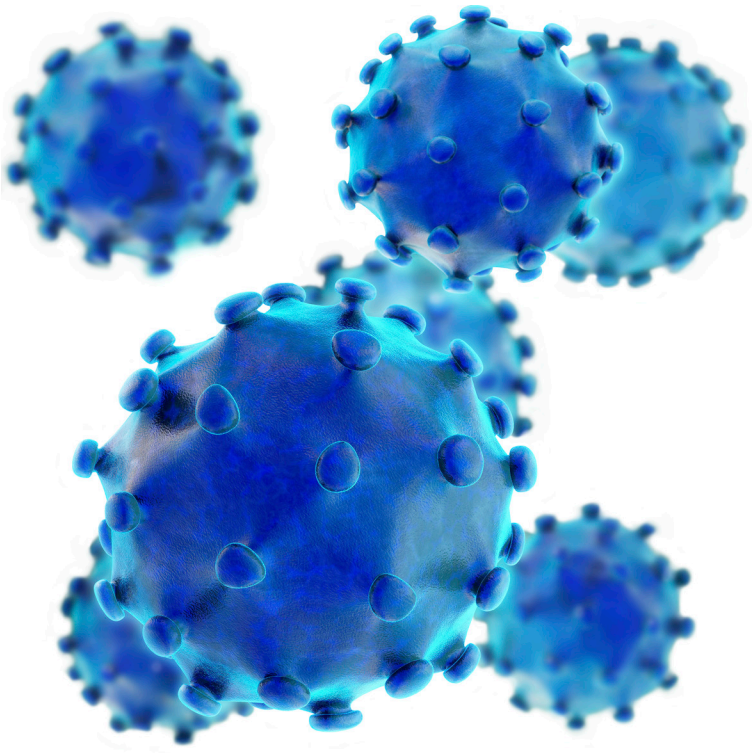
CADTH ISSUES IN EMERGING HEALTH TECHNOLOGY

INFORMING DECISIONS ABOUT NEW HEALTH TECHNOLOGIES

ISSUE 140

OCT 2015

Emerging Oral, Combination, Interferon-Free Regimens for the Treatment of Chronic Hepatitis C Genotype 1



CADTH

CADTH

Author: Ron Pohar

Disclaimer: CADTH Issues in Emerging Health Technologies is a series of bulletins describing health technologies that are not yet used (or widely diffused) in Canada. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada. While the Canadian Agency for Drugs and Technologies in Health (CADTH) has taken care in the preparation of this publication to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this publication or in any of the source documentation.

This document and the information provided in this document are prepared and intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

Copyright © CADTH 2015. You are permitted to reproduce this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Views: The views expressed herein are those of CADTH and do not necessarily reflect the views of our funders.

Cite as: Emerging oral, combination, interferon-free regimens for the treatment of chronic hepatitis C. Ottawa: CADTH; 2015 Oct. (CADTH issues in emerging health technologies; issue 140)

Contact **requests@cadth.ca** with inquiries about this notice or legal matters relating to CADTH services.

ISSN: 1488-6324

Summary

- All-oral, interferon-free regimens for the treatment of chronic hepatitis C genotype 1 are alternatives to the combination of direct-acting antivirals with pegylated interferon and ribavirin.
- These regimens include multiple direct-acting antiviral agents with different mechanisms of action. Of the regimens, only the combinations of ledipasvir and sofosbuvir (Harvoni) and omibitasvir/ paritaprevir/ritonavir and dasabuvir (Holkira) are approved for use in Canada. Other regimens are currently under review by Health Canada and could potentially receive market access in 2015.
- The regimens and findings from phase 2 and 3 clinical trials are summarized in Table 1. While several regimens have been approved for use, others remain in the development stage and, as such, it is uncertain whether they will be marketed in Canada in the future.

The Technology

Oral, interferon-free regimens for the management of genotype 1 chronic hepatitis C (CHC) currently under development consist of combinations of direct-acting antiviral agents (DAAs) that differ in their mechanisms of action, which may reduce the potential for resistance and improve efficacy. The first DAAs approved for the treatment of CHC were boceprevir and telaprevir, both first-generation NS3/4A protease inhibitors (PIs).[1] Boceprevir and telaprevir are used in combination with pegylated interferon and ribavirin (PR), as rapid emergence of resistance can occur with either when used as monotherapy.[2] However, additive adverse effects and poor tolerability are concerns with these triple-therapy regimens.[2] Moreover, cure rates with the first-generation PIs combined with PR remained suboptimal in important subgroups of patients (i.e., those with genotype 1a CHC or cirrhosis, or previous null responders to PR), with sustained virologic response (SVR) rates of 30% to 40%.[2] Telaprevir had been discontinued in Canada, and both boceprevir and telaprevir had been discontinued in the United States.[3,4] Thus, the need for more efficacious, better-tolerated regimens for the management of genotype 1 CHC remained. Initially, the second-generation PI, simeprevir, and first polymerase inhibitor, sofosbuvir, offered some improvement over the first-generation PIs in terms of treatment duration, ease of dosing, and adverse effect profile, but the required co-administration with interferon still presented a burden for patients in terms of tolerability. However, simeprevir and sofosbuvir in combination are now approved for the treatment of CHC genotype 1 without requiring the co-administration of interferon. There are newer DAAs that have recently been approved in Canada, those that are currently under review by Health Canada and others that are under development, that target proteins involved with the replication of the chronic hepatitis C virus (HCV) and include NS5B nucleotide polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A replication complex inhibitors.[2]

Multi-drug, interferon-free, oral regimens of DAAs are currently in various stages of development; some have reached phase 2 and phase 3 clinical trials (Table 2) and a few have reached the stage of regulatory approval. Some combination regimens include ribavirin; however, some are also ribavirin-free.

An optimal treatment regimen for CHC would be pan-genotypic, and have a high efficacy and barrier to resistance while being simple and convenient from the patient perspective. The ideal regimen would also have a favourable adverse effect profile and few drug interactions (for example, with treatments for HIV and tuberculosis, methadone, buprenorphine, statins, hormonal contraception, and psychotropic medications).[5] In addition, characteristics that improve adherence to treatment — including all-oral administration without regard to food, low pill burden, once-daily administration, and an abbreviated treatment duration (preferably 12 weeks or fewer) — are important.[5,6] Furthermore, the regimen ideally would not require pre-treatment testing (interleukin [IL]-28B genotyping, viral subtyping, and drug resistance) or extensive, ongoing monitoring for safety and efficacy.[5]

Regulatory Status

The anticipated timeline for submission and regulatory approval for the majority of regimens outlined in Table 1 could not be determined at the time of writing of this Bulletin.

Ledipasvir 90 mg/sofosbuvir 400 mg (LDV/SOF) — The fixed-dose combination of ledipasvir 90 mg/sofosbuvir 400 mg (LDV/SOF), marketed under the brand name Harvoni, received a Notice of Compliance from Health Canada in October 2014 for the treatment of genotype 1 CHC in adults as a single, once-daily, fixed-dose tablet.[13] Although studied with and without ribavirin, its Health Canada–approved indication does not require treatment in combination with ribavirin.[14]

Sofosbuvir — Sofosbuvir is also available in Canada as a 400 mg tablet (Sovaldi) and approved for the management of genotype 1 CHC in combination with PR or ribavirin alone (see Table 2).[15] Sovaldi is also indicated in the treatment of genotype 4 CHC infection in combination with PR and for the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin alone.[16]

AbbVie 3D combination — The combination of ombitasvir (ABT-267)/paritaprevir (ABT-450)/ritonavir (150 mg/100 mg) once daily co-packaged with 25 mg, dosed once daily, and dasabuvir (ABT-333) 250 mg, dosed twice daily (a regimen referred to as "3D"), was recently approved for use in Canada under the brand name Holkira for patients with genotype 1 CHC as a 12-week regimen for most indications.[17]

Daclatasvir combinations — The combination of daclatasvir with sofosbuvir is approved for use in Europe for genotype 1 CHC.[18] In addition, daclatasvir is currently approved for use in Japan in combination with the protease inhibitor asunaprevir. The approval of daclatasvir is also expected to be pursued in other countries with the exception of the United States, where plans to pursue the regulatory approval of this combination were abandoned.[19] However, the combination of asunaprevir, daclatasvir, and beclabuvir continues to be developed.[20-23]

Simeprevir and sofosbuvir — The combination of simeprevir and sofosbuvir was recently added as an approved indication to the labelling of simeprevir in both Canada and the US.[24] In Canada, simeprevir was issued a Health Canada Notice of Compliance with conditions in January 2015 for use in combination with sofosbuvir for the treatment of genotype 1 CHC in adults with compensated liver disease.[12] Simeprevir is also approved for use in Europe for genotype 1 CHC in combination with sofosbuvir with or without ribavirin.[25] Simeprevir is marketed in Canada as a 150 mg capsule under the brand name Galexos and is also approved for the treatment of genotype 1 CHC in combination with PR.[26]

It is estimated that more than 250,000 Canadians have CHC infection, affecting approximately 1% of the population.[27,28]

Table 1: Summary of Oral, Interferon-Free Treatment Regimens for the Treatment of Chronic Hepatitis C Genotype 1

Regimen and Manufacturer (Brand Name)	Regulatory Status in Canada	Phase (Number of Included RCTs)	Treatment Duration[a]	SVR12
Ledipasvir/sofosbuvir without ribavirin Gilead (Harvoni)	Approved for use	Phase 3 (3) Phase 2 (2)	8 to 24 weeks[b]	93% to 100%
Sofosbuvir with ribavirin Gilead	Approved for use[c]	Phase 2 (1)	24 weeks	48% to 68%[d]
Sofosbuvir/GS-9669 Gilead	Not yet approved	Phase 2 (1)	6 to 12 weeks	68% to 100%
Sofosbuvir/ledipasvir/GS-9669 Gilead	Not yet approved	Phase 2 (1)	8 weeks	82% to 91%
Sofosbuvir/simeprevir Janssen	Approved for use[e]	No studies met the inclusion criteria for the review	12 to 24 weeks[f]	93%[f]
Sofosbuvir/daclatasvir with or without ribavirin BMS	Not yet approved	Phase 2 (1)	12 to 24 weeks	95% to 100%
Sofosbuvir/GS-5816 with or without ribavirin Gilead	Not yet approved	Phase 2 (2)	8 to 24 weeks	81% to 100%
Ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin AbbVie (Holkira Pak)	Approved for use	Phase 3 (4) Phase 2 (1)	12 to 24 weeks[g]	90% to 100%[h]
Ombitasvir/paritaprevir/ritonavir AbbVie	Not yet approved	Phase 2 (1)	12 to 24 weeks	89% to 100%
Daclatasvir/asunaprevir BMS	Not yet approved	Phase 3 (1)	24 weeks	82% to 90%

Table 1: Summary of Oral, Interferon-Free Treatment Regimens for the Treatment of Chronic Hepatitis C Genotype 1 (continued)

Regimen and Manufacturer (Brand Name)	Regulatory Status in Canada	Phase (Number of Included RCTs)	Treatment Duration[a]	SVR12
Daclatasvir, asunaprevir, and beclabuvir with or without ribavirin BMS	Not yet approved	Phase 3 (1)	12 weeks	87% to 98%
Grazoprevir/elbasvir with or without ribavirin Merck	Not yet approved	Phase 2 (1)	8 to 12 weeks	80% to 98%
Daclatasvir and simeprevir with or without ribavirin Janssen BMS	Not yet approved	Phase 2 (1)	12 to 24 weeks	0% to 95%

IU = international unit; RCT = randomized controlled trial; RNA = ribonucleic acid; SVR = sustained virologic response at 12 weeks.

[a] Duration of treatment in the studies included in this Bulletin.

[b] The treatment duration according to Health Canada approval. Eight weeks can be considered in treatment-naive patients who have a hepatitis C RNA < 6 million IU/mL.

[c] Sofosbuvir in combination with ribavirin for 24 weeks can be considered as a therapeutic option for treatment-naive and non-cirrhotic treatment-experienced chronic hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen.[7]

[d] SVR at 24 weeks.

[e] Simeprevir was issued a Health Canada Notice of Compliance with conditions in January 2015 for use in combination with sofosbuvir for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease.

Patient Group

It is estimated that more than 250,000 Canadians have CHC infection, affecting approximately 1% of the population.[27,28] The prevalence of CHC peaks in young to middle-aged adults (those aged 30 to 59 years).[28] There are six main genotypes of HCV, of which the most prevalent in Canada is genotype 1 (approximately 65% of the HCV-infected patient population). There are two subtypes of genotype 1 (1a and 1b), with 1a being more prevalent.[28] Approximately 60% of HCV cases are attributable to current or former use of injection drugs, while approximately 11% of cases are attributable to contaminated blood products.[29]

Acute infection with HCV is most frequently asymptomatic.[30] Following acute infection with HCV, the risk of developing CHC is high, with approximately 50% to 85% of individuals remaining positive for HCV ribonucleic acid (RNA).[30] As with acute infection, CHC is often asymptomatic or is associated with mild, non-specific symptoms. For those with symptoms, fatigue is most common, but less frequent manifestations include nausea, anorexia, myalgia, arthralgia, weakness, and weight loss.[30] Approximately 15% to 20% of individuals with CHC will develop end-stage liver disease over 20 years of infection.[31] All-oral interferon-free regimens may be more efficacious, better tolerated, and more convenient for treatment-naive and treatment-experienced patients and will provide an additional treatment alternative for these patients.

Table 2: Oral Interferon-Free Regimens for Genotype 1 Chronic Hepatitis C in Phase 2 or Phase 3 Clinical Trials

Manufacturer	Combination of Agents					
	NS3/4 Protease Inhibitor	NS5B Nucleotide Polymerase Inhibitor	NS5B Non-Nucleoside Polymerase Inhibitor	NS5A Replication Complex Inhibitor	Ribavirin Included	Phase of Development
Gilead		sofosbuvir		GS-5816	Without	Phase 3
		sofosbuvir			With	Phase 2
		sofosbuvir	GS-9669		Without	Phase 2
		sofosbuvir	GS-9669	ledipasvir	Without	Phase 2
		sofosbuvir		ledipasvir	Without	Phase 3[a]
AbbVie	paritaprevir[b]/ ritonavir		dasabuvir	ombitasvir	With or without	Phase 3[a]
	paritaprevir[b]/ ritonavir		dasabuvir	ABT-530 (for first 3 days) ombitasvir	With	Phase 2
	ABT-493 paritaprevir/ ritonavir[b]		dasabuvir	ombitasvir	With	Phase 3
	ABT-493			ABT-530		Phase 2
Merck	grazoprevir[c]	sofosbuvir		elbasvir[d]	With	Phase 2
	grazoprevir[c]			elbasvir[d]	With or without	Phase 2
Merck BMS	grazoprevir[c]			daclatasvir	Without	Phase 2
Achillion	sovaprevir			ACH-3102	Without	Phase 2
Janssen Idenix Pharmaceuticals	simeprevir			samatasvir[e]	With or without	Phase 2

Table 2: Oral Interferon-Free Regimens for Genotype 1 Chronic Hepatitis C in Phase 2 or Phase 3 Clinical Trials (continued)

Manufacturer	Combination of Agents					
	NS3/4 Protease Inhibitor	NS5B Nucleotide Polymerase Inhibitor	NS5B Non-Nucleoside Polymerase Inhibitor	NS5A Replication Complex Inhibitor	Ribavirin Included	Phase of Development
Janssen BMS	simeprevir			daclatasvir	With or without	Phase 2
BMS	asunaprevir			daclatasvir	Without	Phase 3
	asunaprevir		beclabuvir[f]	daclatasvir	With or without	Phase 3
		sofosbuvir		daclatasvir	Without	Phase 3
Janssen	simeprevir	sofosbuvir			With or without[g]	Phase 3
	simeprevir	sofosbuvir		daclatasvir	Without	Phase 2

[a] Combinations have received Health Canada Notice of Compliance.

[b] Formerly ABT-450.

[c] Formerly MK-5172.

[d] Formerly MK-8742.

[e] Formerly IDX719.

[f] Formerly BMS-791325.

[g] Simeprevir was issued a Health Canada Notice of Compliance with conditions in January 2015 for use in combination with sofosbuvir for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease.[12]

Current Practice

According to the most recent update (2015) of consensus guidelines from the Canadian Association for the Study of the Liver (CASL),[32] all patients with CHC should be considered candidates for antiviral therapy, particularly those with evidence of liver fibrosis.[32] The decision to initiate treatment is based on patient preference and potential risks and benefits of treatment. The goal of antiviral therapy is complete eradication of the virus, as measured by an SVR at least 24 weeks after the end of treatment.[29] The treatment choice for patients with genotype 1 CHC may take into consideration expected efficacy, duration of the regimen, and the adverse effect profile. In addition, the potential for drug interactions, contraindications, comorbid medical conditions, the patient's experience with previous treatment, and the stage of fibrosis are considerations.[33]

The 2015 update to the CASL guidelines recommends the use of all-oral interferon-free regimens as first-line therapy for treatment-naive and treatment-experienced patients with genotype 1 CHC.[32] This includes the combination of ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni) and the AbbVie 3D combination (Holkira Pak). At the same time, the guidelines recognize that access to such regimens may not be universal across Canada and that other factors, such as the patient's wishes, the severity of liver disease, and the potential to tolerate PR, are also considerations.[32] Recent Canadian guidelines for the treatment of HIV/HCV coinfection[34] recommend the combinations of simeprevir and sofosbuvir and sofosbuvir with ribavirin as alternatives for treatment-naive patients with genotype 1 CHC without cirrhosis. For treatment-naive patients with cirrhosis, simeprevir and sofosbuvir is also recommended as an alternative.

Methods

Literature Search

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, and Embase. Grey literature was identified by selectively searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). No filters were applied to limit the retrieval by study type. The search was limited to English-language documents published between January 1, 2012 and September 15, 2014. Regular alerts were established to update the search until February 23, 2015.

Study Selection

Phase 2 or 3 randomized controlled clinical trials, published in full or as conference abstracts, that compared interferon-free oral regimens with placebo or an active comparator (consisting of PR alone or in combination with a DAA) in adults with genotype 1 CHC were selected for inclusion. Open-label extension trials were not included, nor were interim reports of phase 2 or phase 3 randomized controlled trials (RCTs), studies in which patients received treatment for less than one week, or studies that compared only the identical regimen with a different duration of treatment (as per Table 3). The proof-of-concept phase 2a studies were excluded. However, those phase 2 studies that did not specify whether the trial phase was 2a or 2b were included.

The Evidence

Efficacy

Phase 2 and phase 3 RCTs of all-oral, interferon-free regimens for genotype 1 CHC are summarized in Appendix A, including study design, patient populations, treatment regimens, SVR at 12 and 24 weeks (where reported), and a summary of the key limitations. The key limitations were similar for the included studies (Appendix A) and were mainly related to the generalizability of the findings, the open-label designs, and the use of historical controls. Some studies excluded patients with HIV or hepatitis B coinfection and cirrhosis; thus, the SVR that was achieved may not be applicable to those populations. Exclusion of patients based on previous adverse reactions may also affect the generalizability of a few studies,[35-37] as this may have led to the selection of patients less likely to experience an adverse reaction. In some studies, particularly those with multiple treatment arms, the number of participants in each arm was relatively small, which could limit their study power in identifying rare adverse events. While the outcome

Table 3: Selection Criteria for Phase 2 and Phase 3 Studies of Oral, Interferon-Free Regimens for Genotype 1 Chronic Hepatitis C

Populations	Adult patients with genotype 1 CHC Mixed populations of multiple genotypes; provided data for genotype 1 CHC were reported separately
Interventions	Interferon-free regimens in phase 2b or 3 clinical stage development
Comparators	Placebo Active comparators (e.g., PR or PR + DAA)
Outcomes	SVR, adverse effects
Study Design	Inclusion: Phase 2b or 3 randomized controlled clinical trials, published in full or as conference abstracts Exclusion: Open-label extension trials, interim reports of results, proof-of-concept studies of limited duration (e.g., fewer than 7 days of treatment)

CHC = chronic hepatitis C; DAA = direct-acting antiviral; PR = pegylated interferon and ribavirin; SVR = sustained virologic response.

of SVR may be objective, reporting of adverse events could potentially be influenced by knowledge of treatment, as could patient-reported outcomes (reported in only one study[38]). In some studies, participants were first randomized to a blinded placebo arm, then treated with the active drug so that the adverse events associated with the investigational product could be evaluated against those of the untreated condition. The use of the historical control has some important limitations. Comparison with a historical control is not equivalent to randomizing participants to a treatment or control group and then making a statistical comparison between the groups. Further, given that the characteristics of the historical controls were not reported, it is unclear how similar the historical control patients and study participants would be, thereby decreasing confidence in the findings. Moreover, it is not clear that the treatment received by the historical control aligns with current practice. Thus, the relevance of a comparison with these treatment regimens is unclear.

Ledipasvir/Sofosbuvir With and Without Ribavirin (Harvoni)

Four phase 2 or 3, open-label RCTs[35,36,38,39] (ION-1, ION-2, ION-3, and LONESTAR) and one double-blind RCT[40] met the selection criteria in which a fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) was evaluated with and without ribavirin (see Appendix A). Across the five studies, the combination was assessed in treatment-naive and treatment-experienced populations, with study outcomes assessed and analyzed separately for these groups. The studies were conducted in the US,[35,36,38,39] Europe,[38] and France.[40] Durations of treatment ranged from eight weeks to 24 weeks, with the SVR evaluated at 12 weeks (SVR12) in most studies. The SVR12 ranged from 93% to 100% and was numerically similar between eight-, 12-, and 24-week durations of treatment. The SVR was similar between treatment arms that did and did not receive ribavirin.

Sofosbuvir With Ribavirin

One phase 2 open-label RCT compared sofosbuvir in combination with two different regimens of ribavirin (standard and low-dose).[41] The study was conducted in the US and included only treatment-naive patients who were seronegative for HIV and hepatitis B. The duration of treatment was 24 weeks. The SVR12 was 68% with standard dosing of ribavirin and 48% with low-dose ribavirin (see Appendix A).

Sofosbuvir and GS-9669 Compared With Ledipasvir/Sofosbuvir

The combination of sofosbuvir and GS-9669 was compared with LDV/SOF in treatment-naive and treatment-experienced patients with genotype 1 CHC, in a phase 2, open-label RCT (ELECTRON) conducted in New Zealand.[42] The duration of treatment was 12 weeks. All LDV/SOF and GS-9669 plus SOF groups received ribavirin as part of the regimen, with the exception of one group of treatment-experienced patients with cirrhosis, who were treated with LDV/SOF alone for 12 weeks. In addition, one treatment-naive arm received LDV/SOF with ribavirin for six weeks, rather than 12 weeks. In treatment-naive and treatment-experienced patients, the SVR12 was 100% both in the LDV/SOF group and the SOF plus GS-9669 group. The SVR12 was 68% (95% confidence interval [CI], 47% to 85%) with six weeks of LDV/SOF in the treatment-naive population. In treatment-experienced patients, LDV/SOF with ribavirin was compared with LDV/SOF alone, and it was found that the SVR12 was lower in the absence of ribavirin (70% with LDV/SOF alone versus 100% for LDV/SOF with ribavirin).

Ledipasvir/Sofosbuvir with GS-9669 Compared With Ledipasvir/Sofosbuvir and Ribavirin

The combination of SOF, GS-9669 (250 mg or 500 mg), and LDV (two arms) was compared with LDV/SOF and ribavirin (one arm) in a US-based phase 2 open-label RCT that included patients with genotype 1 CHC and compensated cirrhosis.[43] Patients in all arms were treated for eight weeks. The SVR12 was 82% in the sofosbuvir, GS-9669 500 mg, and LDV arm; 89% in the LDV/SOF with ribavirin (RBV) arm; and 91% in the arm received sofosbuvir, GS-9669 250 mg, and LDV (see Appendix A).

Sofosbuvir and Daclatasvir With or Without Ribavirin

In a US-based phase 2, open-label RCT that included treatment-naive and treatment-experienced patients with genotype 1 CHC, combinations of sofosbuvir and daclatasvir (SOF/DCV) with and without ribavirin were compared (see Appendix A).[37] Treatment regimens with durations of 12 and 24 weeks were assessed. The SVR12 ranged from 95% to 100% and was similar in groups that did and did not receive ribavirin, and in treatment-naive and treatment-experienced patients. The SVR24 was reported for treatment-experienced patients and ranged from 93% (SOF/DCV with ribavirin for 12 weeks) to 100% (SOF/DCV with and without ribavirin for 24 weeks).

Sofosbuvir and GS-5816 With or Without Ribavirin

Multiple dosages of GS-5816 in combination with sofosbuvir (with or without ribavirin) were compared in treatment-naive patients without cirrhosis for eight- and 12-week durations in two open-label phase 2 RCTs (see Appendix A).[44,45] For the eight-week regimens,[44] the SVR12 ranged from 81% to 90%, while the SVR12 ranged from 96% (SOF/GS-5816 25 mg without ribavirin) to 100% (SOF/GS-5816 100 mg without ribavirin) with 12 weeks of treatment.

Ombitasvir/Paritaprevir (ABT-450)/Ritonavir

The combination of paritaprevir/ritonavir with ombitasvir was evaluated in one open-label phase 2 study conducted in Japan (see Appendix A).[46] The study included treatment-experienced, non-cirrhotic patients with genotype 1b CHC. Four treatment regimens were assessed that differed in the dosage of paritaprevir (100 mg versus 150 mg) and duration of treatment (12 weeks versus 24 weeks). In the treatment arms that received ombitasvir with paritaprevir/ritonavir 100 mg/100 mg for 12 weeks and 24 weeks, the SVR12 was 100%. In the treatment arms that received ombitasvir with paritaprevir/ritonavir 150 mg/100 mg, the SVR12 was 89% with 12 weeks' duration of therapy, but 100% with 24 weeks' duration.

Ombitasvir/Paritaprevir (ABT-450)/Ritonavir and Dasabuvir (Holkira Pak) With or Without Ribavirin

The combination of paritaprevir/ritonavir, dasabuvir, and ombitasvir (referred to as "3D" and marketed in Canada under the brand name Holkira Pak) has been evaluated in one phase 2b[47] (AVIATOR) and three phase 3, non-inferiority, open-label (PEARL-II) and double-blind (PEARL-III, and PEARL-IV) RCTs,[8,9] as well as two randomized, double-blind placebo-controlled trials[10,11] (SAPPHIRE-I and SAPPHIRE-II) conducted in Canada, the US, Europe, and the United Kingdom (see Appendix A). The studies included both treatment-experienced and treatment-naive non-cirrhotic patients with genotype 1 CHC. Treatment regimens of 12 weeks were evaluated in all studies, with the 3D combination being assessed alone or with ribavirin. In one study, eight- and 24-week regimens were also evaluated (AVIATOR).[47] SVR12 rates ranged from 90% to 100%. SVR24 rates ranged from 83% to 100% in the phase 2b study (AVIATOR).[47] Three studies that assessed the non-inferiority of the 3D combination alone compared with the 3D combination with ribavirin found that 3D alone was non-inferior.[8,9]

Daclatasvir and Asunaprevir

The HALLMARK DUAL study[48] was an international phase 3 study that included four treatment arms in total. Treatment-naive patients with genotype 1b CHC were randomized in a 2:1 ratio to receive daclatasvir and asunaprevir or placebo; however, no results were reported for the placebo group. The other two treatment arms (non-responders and patients ineligible for or intolerant to PR) received open-label daclatasvir and asunaprevir, with no comparator. The SVR12 in both of these groups was 82% (95% CI, 77% to 87%). In treatment-naive patients, the SVR12 was 90% (95% CI, 85% to 94%).

Daclatasvir, Asunaprevir, and Beclabuvir With or Without Ribavirin

The UNITY-2 study was an international phase 3 RCT that compared daclatasvir, asunaprevir, beclabuvir, and RBV with daclatasvir, asunaprevir, beclabuvir, and placebo in treatment-naive and treatment-experienced patients with genotype 1 CHC and compensated cirrhosis (see Appendix A).[20] Patients in all arms received 12 weeks of treatment. In treatment-naive patients, the SVR12 was 93% in the arm without ribavirin and 98% in the ribavirin arm, while in treatment-experienced patients, the SVR12 was 87% in the arm without ribavirin and 93% in the ribavirin arm.

Grazoprevir/Elbasvir With or Without Ribavirin

An open-label phase 2 study (C-WORTHY Part B) assessed the efficacy of the combination of grazoprevir/elbasvir with or without ribavirin in four different groups of patients with genotype 1 CHC: treatment-naive patients with HIV; treatment-naive patients without HIV; treatment-naive patients with cirrhosis; and null responders with or without cirrhosis.[49,50] Results were published in two different reports (see Appendix A).[49,50] For the first two treatment arms, eight- and 12-week regimens were assessed in the monoinfected population, while the HIV-coinfected population was treated for 12 weeks only.[49] The SVR12 ranged from 80% (in the eight-week regimen) up to 98% in the other treatment arms. Treatment regimens of 12 and 18 weeks were also assessed in treatment-naive patients with cirrhosis and in null responders with or without cirrhosis.[50] In previously treated patients with cirrhosis, the SVR12 ranged from 90% to 94%, while in null responders with or without cirrhosis, the SVR12 ranged from 91% to 100%.[50]

Daclatasvir and Simeprevir With or Without Ribavirin

The efficacy of the combination of daclatasvir and simeprevir (SMV) with or without ribavirin was assessed in treatment-naive and treatment-experienced patients (null responders) in a phase 2, open-label RCT (LEAGUE-I).[51] The duration of treatment was for 12 or 24 weeks (see Appendix A). The results were presented in an abstract in which it was unclear whether the outcomes reported were for 12- or 24-week treatment regimens. In treatment-naive patients, the SVR12 ranged from 75% to 85%, with the lower SVR being for the combination with ribavirin. No explanation was provided for this finding. For null responders, the SVR12 was 0% for genotype 1a (treated with DCV and SMV and RBV), 65% for genotype 1b treated with DCV plus SMV, and 95% for genotype 1b treated with DCV plus SMV and RBV. It should be noted that the dose of DCV used in the LEAGUE-1 study was 30 mg, due to a drug interaction with SMV, which was expected to increase DCV exposure two-fold. However, ongoing trials of DCV plus SMV are using a 60 mg dose, as the increase in DCV exposure related to the drug interaction was not as large as originally anticipated.[52]

Adverse Effects

The most frequently observed adverse effects reported in clinical trials of oral interferon-free regimens for genotype 1 CHC are summarized in Table 4. Overall, headache, fatigue, and nausea were the most frequently observed.

Administration and Cost

The antiviral regimens included in this Bulletin were all administered orally, requiring once- or twice-daily dosing. The pill burden would be expected to differ to some extent across regimens, although co-formulated tablets that include two or three different drugs have been used in trials, which simplifies the regimens somewhat. The combination of LDV/SOF (Harvoni) is administered as a once-daily, single tablet, whereas Holkira (3D regimen) is administered as two tablets (ombitasvir/paritaprevir/ritonavir co-formulation) taken once daily and one tablet (dasabuvir) twice daily. However, for many regimens, the number of tablets or dosing times required for each regimen was unclear from the study descriptions. In addition, it is possible that later in the development of the all-oral interferon-free regimens, co-formulations will be introduced to reduce the pill burden. Thus, comparison of pill burden across regimens is premature at present. For those regimens that have not yet been approved by Health Canada, the cost of the regimens has not yet been determined. The cost of Harvoni in Canada is approximately $798 per tablet, and $44,667 and $67,000 for the eight-week and 12-week regimens, respectively.[55] The cost of Sovaldi (sofosbuvir alone) is $655 per tablet[55] and Galexos (simeprevir) is $435 per capsule.[55] This would make the cost of a 12-week course of the combination simeprevir/sofosbuvir $91,560. The cost of Holkira Pak in Canada is $665 per daily pack and $58,653 to 117,306 for the annual cost of therapy.[56]

The cost of the all-oral, interferon-free regimens may potentially be a barrier to treatment for many patients in the absence of reimbursement by third-party payers.

Concurrent Developments

In addition to the regimens listed in Table 2, other all-oral regimens for the CHC virus that are in development are listed in Appendix B. Appendix B also lists ongoing studies for several of the regimens from Table 2 that do not have trial results reported.

Rate of Technology Diffusion

Compared with the current standard regimens that include PR, all-oral, interferon-free regimens have advantages in terms of convenience, potential for improved adherence related to oral administration, shorter duration of treatment, and favourable adverse effect profiles, and these advantages may contribute to rapid uptake of these regimens. There is also no need for interferon, which is attractive given interferon's unfavourable impact in terms of adverse effects and quality of life. In addition, there may be a clinical advantage of increased rates of SVR 12 to 24 weeks after treatment, based on clinical trial evidence. There may be a potential for off-label use of DAAs that are active against other genotypes of HCV, in addition to genotype 1. The majority of included phase 2 and phase 3 RCTs excluded certain populations, such as HIV- or hepatitis B–coinfected patients or patients with cirrhosis. However, data from the HIV-coinfected population in the C-WORTHY study suggest

SVR rates and adverse events that are similar to monoinfected patients.[49] Further, in the TURQUOISE-II study, which included only patients with genotype 1 CHC and cirrhosis, ombitasvir/paritaprevir/ritonavir and dasabuvir (3D regimen) demonstrated SVR rates superior to a historical control and infrequent discontinuations due to adverse effects.[57] Despite limited RCT evidence, it is possible that oral agents will be used in these populations. Studies for some all-oral, interferon-free regimens are ongoing in more specific populations, such as those with cirrhosis and HIV coinfection (see Appendix B). Observational or non-randomized studies or RCTs assessing the safety and efficacy in these excluded populations are currently ongoing, so adoption in populations outside of the scope of the trials included in this Bulletin remains a possibility.

Table 4: Most Frequently Observed Adverse Effects Reported in Clinical Trials of Oral Interferon-Free Regimens for Genotype 1 Chronic Hepatitis C

Ledipasvir/sofosbuvir with and without ribavirin	ION-1[53] Headache (25%), fatigue (23%), and nausea (12%) ION-2[35] Headache (26% to 32%), fatigue (21% to 45%), and nausea (6% to 23%) ION-3[39] Headache (14% to 25%), fatigue (21% to 35%), and nausea (7% to 18%) LONESTAR[36] Headache (5% to 14%), nausea (0% to 10%), and decreased appetite (0% to 10%)
Sofosbuvir with ribavirin	Osinusi[41] Headache (28%), anemia (16% to 32%), fatigue (16% to 24%), and nausea (16% to 24%)
Sofosbuvir and GS-9669	ELECTRON[42] Headache (22% to 67%), fatigue (10% to 78%), and nausea (0% to 44%)
Sofosbuvir/ledipasvir and GS-9669	Headache, diarrhea, and nausea (data not reported)
Sofosbuvir and daclatasvir with or without ribavirin	Sulkowski[37] Fatigue (29% to 50%), headache (16% to 38%), and nausea (0% to 32%)
Sofosbuvir and GS-5816 with or without ribavirin	Tran 2014[44] Fatigue, headache, and nausea (> 10%) Pianko 2014[45] Fatigue, headache, nausea, and insomnia (> 10%)
Ombitasvir/paritaprevir/ritonavir	Chayama[46] Headache (6% to 16%), back pain (11% to 17%), diarrhea (0% to 17%), vomiting (0% to 17%)

Table 4: Most Frequently Observed Adverse Effects Reported in Clinical Trials of Oral Interferon-Free Regimens for Genotype 1 Chronic Hepatitis C (continued)

Ombitasvir/paritaprevir/ ritonavir and dasabuvir with or without ribavirin	PEARL-II[8] Fatigue (16% to 32%), headache (23% to 24%), and nausea (6% to 29%) PEARL-III and PEARL-IV[9] Headache (23% to 28%), nausea (4% to 21%), fatigue (21% to 46%), pruritus (5% to 12%), and insomnia (3% to 17%) SAPPHIRE-I[10] Fatigue (29% to 35%), headache (27% to 33%), and nausea (13% to 24%) SAPPHIRE-II[11] Fatigue (23% to 33%), headache (35% to 36%), and nausea (18% to 20%) AVIATOR[47] Fatigue (21% to 36%), headache (19% to 35%), and nausea (13% to 25%)
Daclatasvir and asunaprevir without ribavirin	HALLMARK DUAL[48] Headache (20% to 25%), fatigue (17% to 22%), diarrhea (11% to 22%), and nausea (11% to 12%)
Daclatasvir, asunaprevir, and beclabuvir with or without ribavirin	UNITY-2[20] Fatigue, headache, nausea, diarrhea, insomnia, and pruritus (> 10% of patients)
Grazoprevir, elbasvir with or without ribavirin	C-WORTHY[49,50] Fatigue (7% to 47%), headache (3% to 35%), and nausea (0% to 27%)
Daclatasvir and simeprevir with or without ribavirin	LEAGUE-1[54] Most common adverse effects not reported.

The cost of the all-oral, interferon-free regimens may potentially be a barrier to treatment for many patients in the absence of reimbursement by third-party payers. It is conceivable that manufacturers may establish programs to facilitate financial access to these regimens for treatment-eligible patients who require such assistance. Gilead, the manufacturer of Harvoni, is currently offering such a program.[13]

Implementation Issues

The availability of treatment options for genotype 1 CHC is changing quickly. With numerous oral, interferon-free regimens either already on the Canadian market or in development, there is the potential for multiple treatment options to be available. Due to the rapidly changing landscape, treatment guidelines for regimen selection, sequence, and individualization of therapy based on response may lag behind clinical practice for the foreseeable future. Care will have to be provided by a highly knowledgeable team, and frequent monitoring and follow-up will be needed to optimize treatment. It is possible that there will be regional, knowledge, and infrastructure gaps. The guidelines from CASL state that all patients should be considered as candidates for antiviral therapy.[32] However, high drug cost remains a barrier for treatment access. In addition, accessibility to accurate, non-invasive means of liver fibrosis assessment across jurisdictions has been identified in the guidelines as critical to the treatment of CHC.[32] Current gaps in the evidence include the safety and efficacy of the all-oral interferon-free regimens in subgroups, such as those with HIV or hepatitis B coinfection, and salvage treatment options for patients who do not achieve an SVR following all-oral interferon-free therapy.

References

1. Foster GR, De Silva S. Hepatitis C genotype 1. Curr Opin Infect Dis. 2014 Dec;27(6):535-9.
2. Yau AH, Yoshida EM. Hepatitis C drugs: the end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: a concise review. Can J Gastroenterol Hepatol. 2014 Sep;28(8):445-51.
3. HIVandHepatitis.com [Internet]. Merck plans to discontinue boceprevir for hepatitis C by December 2015; 2015 Jan 21 [cited 2015 Mar 3]. Available from: http://www.hivandhepatitis.com/hcv-treatment/approved-hcv-drugs/5021-merck-plans-to-discontinue-boceprevir-for-hepatitis-c-by-december-2015
4. HIVandHepatitis.com [Internet]. Vertex to discontinue sale of telaprevir (Incivek) for hepatitis C; 2014 Aug 22 [cited 2015 Mar 3]. Available from: http://www.hivandhepatitis.com/hcv-treatment/approved-hcv-drugs/4808-vertex-to-discontinue-sale-of-telaprevir-incivek-for-hepatitis-c
5. Swan T. Hepatitis C development catapults onward [Internet]. New York: Treatment Action Group; 2013. [cited 2014 Dec 17]. Available from: http://www.pipelinereport.org/sites/g/files/g575521/f/201306/HCV.pdf
6. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. Liver Int. 2014 Feb;34 Suppl 1:69-78.
7. PrSovaldi® (sofosbuvir) tablets, 400 mg sofosbuvir [product monograph]. Foster City (CA) and Mississauga (ON): Gilead Sciences Inc. and Gilead Sciences Canada Inc.; 2014 Dec 4. Submision Control No.: 175080.
8. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology. 2014 Aug;147(2):359-65.
9. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014 May 22;370(21):1983-92.
10. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1594-603.
11. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1604-14.
12. PrGalexos® simeprevir capsules, 150 mg simeprevir (as simeprevir sodium) [product monograph]. Toronto: Janssen Inc; 2015 Jan 29. Submission Control No: 176169.
13. Health Canada issues notice of compliance for Gilead's Harvoni™ (ledispasvir/sofosbuvir), the first once-daily single tablet regiment for the treatment of genotype 1 chronic hepatitis C [Internet]. Foster City (CA): Gilead Sciences, Inc.; 2014 Oct 14. [cited 2014 Nov 5]. Available from: http://www.gilead.com/news/press-releases/2014/10/health-canada-issues-notice-of-compliance-for-gileads-harvoni-ledipasvirsofosbuvir-the-first-oncedaily-single-tablet-regimen-for-the-treatment-of-genotype-1-chronic-hepatitis-c
14. PrHarvoni™ (ledispasvir/sofosbuvir): tablets 90 mg/400 mg [product monograph]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2014 Oct 14.
15. PrSovaldi® (sofosbuvir) tablets, 400 mg sofosbuvir antiviral agent [product monograph]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2014 Sep 30.
16. Health Canada. Summary basis of decision (SBD) for Sovaldi. Sofosbuvir, 400 mg, tablet, oral. Drug identification number (DIN): 02418355. Gilead Sciences Canada Inc. New drug submission control number: 165043 [Internet]. Ottawa: Health Canada, Health Products and Food Branch; 2014 Feb 18. [cited 2015 Jan 20]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_sovaldi_165043-eng.php#sbd
17. AbbVie receives Health Canada approval of Holkira™ Pak for the treatment of chronic genotype 1 hepatitis C [Internet]. Montreal: CNW Group Ltd.; 2014 Dec 23. [cited 2015 Jan 2]. Available from: http://www.newswire.ca/en/story/1467193/abbvie-receives-health-canada-approval-of-holkiratm-pak-for-the-treatment-of-chronic-genotype-1-hepatitis-c
18. Daklinza: EPAR - product information [Internet]. London: European Medicines Agency; 2014. [cited 2014 Nov 5]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003768/WC500172848.pdf
19. Bristol-Myers Squibb statement about asunaprevir in the U.S. [Internet]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Oct 7. [cited 2014 Nov 5]. Available from: http://news.bms.com/press-release/rd-news/bristol-myers-squibb-statement-about-asunaprevir-us
20. Muir A, Poordad F, Lalezari JP, Everson GT, Dore GJ, Kwo P, et al. All-oral fixed-dose combination therapy with daclatasvir/asunaprevir/BMS-791325, ± ribavirin, for patients with chronic HCV genotype 1 infection and compensated cirrhosis: UNITY-2 phase 3 SVR12 results [Internet]. Abstract presented at: American Association for the Study of Liver Diseases (AASLD). 2014 Nov 7-11; Boston. [cited 2014 Dec 17]. Available from: http://aasld.multieposter.com/2014/LB-2.pdf Late-breaking abstract LB-2.
21. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02123654, UNITY 3: a Japanese phase 3 study of a daclatasvir/asunaprevir/BMS-791325 in subjects with genotype 1 chronic hepatitis C; 2014 [cited 2014 Dec 17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02123654
22. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02170727, A phase 3 study of a daclatasvir/asunaprevir/BMS-791325 fixed dose combination (FDC) in subjects with chronic hepatitis C genotype 1 (UNITY 4); 2014 [cited 2014 Dec 17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02170727
23. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01979939, UNITY 1: a study of an investigational treatment regimen of daclatasvir (DCV) + asunaprevir (ASV) + BMS-791325 in a fixed dose combination (the DCV 3DAA (direct acting antiviral) regimen) for 12 weeks for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection in non-cirrhotic subjects; 2014 [cited 2014 Dec 17]. Available from: https://clinicaltrials.gov/ct2/show/NCT01979939
24. Klein R, Struble K, Morin S. FDA hepatitis update: changes to Olysio (simeprevir) label. HCV New Drug Research [Internet]. 2014 Nov 5 [cited 2014 Nov 7]. Available from: http://hepatitiscnewdrugs.blogspot.ca/2014/11/fda-hepatitis-update-changes-to-olysio.html

25. Olysio (simeprevir) [Internet]. London: European Medicines Agency; 2014. [cited 2014 Nov 5]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002777/human_med_001766.jsp&mid=WC0b01ac058001d124

26. PrGalexos™ simeprevir capsules: 150 mg simeprevir (as simeprevir sodium) [product monograph]. Toronto: Janssen Inc.; 2014 Jul 7.

27. MacParland SA, Bilodeau M, Grebely J, Bruneau J, Cooper C, Klein M, et al. The 3rd Canadian Symposium on Hepatitis C Virus: expanding care in the interferon-free era. Can J Gastroenterol Hepatol. 2014 Oct;28(9):481-7.

28. Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol [Internet]. 2014 May [cited 2014 Nov 5];28(5):243-50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049256/pdf/cjgh-28-05-243.pdf

29. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol [Internet]. 2012 Jun [cited 2014 Nov 6];26(6):359-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378284

30. Chopra S. Clinical manifestations and natural history of chronic hepatitis C virus infection. 2014 Oct 27 [cited 2014 Nov 6]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: www.uptodate.com Subscription required.

31. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418-31.

32. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. An update on the management of chronic hepatitis C: 2015 consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol [Internet]. 2015 Jan [cited 2015 Mar 3]. Available from: http://www.liver.ca/files/Professional_Education___Partnerships/Information___Resources_for_HCP/CASL_Hep_C_Consensus_Guidelines_Update_-_Jan_2015.pdf

33. Chopra S, Muir AJ. Treatment regimens for chronic hepatitis C virus genotype 1. 2014 Oct 27 [cited 2014 Nov 6]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: www.uptodate.com Subscription required.

34. Hull M, Shafran S, Tseng A, Giguere P, Klein MB, Cooper C. CIHR Canadian HIV Trials Network Co-Infection and Concurrent Diseases Core: updated Canadian guidelines for the treatment of hepatitis C infection in HIV-hepatitis C coinfected adults. Can J Infect Dis Med Microbiol [Internet]. 2014 Nov [cited 2015 Mar 25];25(6):311-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4277159

35. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.

36. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014 Feb 8;383(9916):515-23.

37. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211-21.

38. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889-98.

39. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879-88.

40. Bourlière J, Bronowicki J, de Ledinghen V, Hezode C, Zoulim F, Mathurin P. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy [abstract]. Hepatology. 2014;60(1 Suppl):LB-6.

41. Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013 Aug 28;310(8):804-11.

42. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology. 2014 Mar;146(3):736-43.

43. Lawitz E, Poordad F, Hyland RH, Wang J, Pang PS, Symonds WT, et al. High rates of SVR in patients with genotype 1 HCV infection and cirrhosis after treatment with ledipasvir/sofosbuvir+ribavirin or ledipasvir/sofosbuvir+ GS-9669 for 8 weeks [abstract]. Hepatology. 2014;60:1143A.

44. Tran TT, Morgan TR, Thuluvath PJ, Etzkorn K, Hinestrosa F. Safety and efficacy of treatment with sofosbuvir + GS-5816 ± ribavirin for 8 or 12 weeks in treatment naïve patients with genotype 1-6 HCV infection [abstract]. Hepatology. 2014 Oct;60(4 Suppl):237A.

45. Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, et al. High efficacy of treatment with sofosbuvir+GS-5816 +ribavirin for 12 weeks in treatment experienced patients with genotype 1 or 3 HCV infection [abstract]. Hepatology. 2014;60:297A-98A.

46. Chayama K, Notsumata K, Kurosaki M, Sato K, Rodrigues-Jr L, Setze C, et al. Randomized trial of interferon- and ribavirin-free ombitasvir/paritaprevir/ritonavir in treatment-experienced hcv-infected patients. Hepatology. 2015 Jan 16.

47. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med. 2014 Jan 16;370(3):222-32.

48. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet. 2014 Nov 1;384(9954):1597-605.

49. Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2014 Nov 11. Epub ahead of print.

50. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2014 Nov 11. Epub ahead of print.

51. Zeuzem S, Hezode C, Bronowicki JPP, Loustad-Ratti V, Gea F, Buti M, et al. Daclatasvir in combination with simeprevir + ribavirin for hepatitis C virus genotype 1 infection [abstract]. Topics in Antiviral Medicine. 2014 Apr;22(e-1):15-6.

52. Highleyman L. CROI 2014: daclatasvir + simeprevir effective against hepatitis C genotype 1b [Internet]. San Francisco (CA): HIVandHepatitis.com; 2014 Mar 11. [cited 2015 Apr 29]. Available from: http://www.hivandhepatitis.com/hcv-treatment/experimental-hcv-drugs/4577-croi-2014-daclatasvir-simeprevir-effective-against-hepatitis-c-genotype-1b

53. Mangia A, Marcellin P, Kwo P, Foster GR, Buti M, Bräu N, et al. All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-naive genotype 1 HCV-infected patients: the phase 3 ION-1 study [abstract]. J Hepatol. 2014;60(1 Suppl 1):S523-24.

54. Sulkowski M, Mallolas J, Bourliere M, Gerstoft J, Shibolet O, Nahass R, et al. On-treatment viral response to MK-5172/MK-8742 + RBV for 12 weeks in HCV/HIV-coinfected patients [abstract]. Topics in Antiviral Medicine. 2014 Apr;22(e-1):324-25.

55. Drug Plan and Extended Benefits Branch. Saskatchewan online formulary database [Internet]. Regina: Government of Saskatchewan; 2015 [cited 2015 Apr 29]. Available from: http://formulary.drugplan.health.gov.sk.ca/

56. BC PharmaCare drug information sheet for ombitasvir-paritaprevir-ritonavir and dasabuvir (Holkira™ Pak) [Internet]. Victoria: British Columbia Ministry of Health, Medical Beneficiary and Pharmaceutical Services Division; 2015. [cited 2015 Jun 2]. Available from: http://www2.gov.bc.ca/gov/DownloadAsset?assetId=CF913556ED0C4F2B9B1AD-50F95EA3AA1&filename=holkira-pak-3375-info.pdf

57. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014 May 22;370(21):1973-82.

58. Younossi Z, Stepanova M, Marcellin P, Afdhal N, Nader F, Hunt S. Ledipasvir (LDV) and sofosbuvir (SOF) combination improves patient-reported outcomes (PRO) during treatment of chronic hepatitis C (CH-C) patients: results from the ION-1 clinical trial [abstract]. J Hepatol. 2014;60(1 Suppl 1):S536-S537.

59. Bourliere M, Bronowicki JP, de Ledinghen V, Hezode C, Zoulim F, Mathurin P, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015 Apr;15(4):397-404.

60. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02168361, The SIM-SOF trial for hepatitis C; 2014 Jun 19 [cited 2014 Nov 5]. Available from: http://clinicaltrials.gov/show/NCT02168361

61. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02262728, An efficacy, safety and pharmacokinetics study of simeprevir, daclatasvir and sofosbuvir in participants with chronic hepatitis C virus genotype 1 or 4 infection and decompensated liver disease; 2015 Feb 13 [cited 2015 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT02262728

62. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02349048, Study to assess efficacy, safety, tolerability and pharmacokinetics of simeprevir, daclatasvir and sofosbuvir in treatment-naive participants with chronic hepatitis C virus genotype 1 infection (ACCORDION-1); 2015 Feb 9 [cited 2015 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT02349048

63. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02165189, An efficacy and safety study of simeprevir and sofosbuvir with and without ribavirin in participants with recurrent genotype 1 hepatitis C post-orthotopic liver transplant (GALAXY); 2015 Feb 19 [cited 2015 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT02165189

64. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01852604, Samatasvir IDX719 in combinations with simeprevir and/or TMC647055/ritonavir with or without ribavirin for 12 weeks in subjects with chronic hepatitis C infection (MK-1894-005); 2015 Mar 2 [cited 2014 Nov 5]. Available from: http://clinicaltrials.gov/show/NCT01852604

65. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02268864, A study to assess the efficacy and safety of the combination of simeprevir and daclatasvir in chronic hepatitis C genotype 1b-infected participants with advanced liver disease (COMMIT); 2015 Feb 3 [cited 2015 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT02268864

66. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01938625, A study of pharmacokinetics, efficacy, safety, tolerability, of the combination of simeprevir (TMC435), daclatasvir (BMS-790052), and Rrbavirin (RBV) in patients with recurrent chronic hepatitis C genotype 1b infection after orthotopic liver transplantation; 2015 Feb 2 [cited 2015 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT01938625

67. Lawitz E, Rodriguez-Torres M, Nguyen TT, Sheikh AM, Tobias H, Galati JS, et al. HELIX-2, a phase II study of samatasvir in combination with simeprevir, low dose ritonavir-boosted TMC647055 + ribavirin in treatment-naive or interferon/ribavirin treated, relapsed genotype 1 HCV-infected subjects [abstract]. Hepatology. 2014;60:1138A.

68. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01849562, Safety, tolerability and efficacy of 12-weeks of sovaprevir, ACH-3102 and ribavirin in treatment-naive GT-1 HCV subjects; 2014 Aug 26 [cited 2014 Nov 5]. Available from: http://clinicaltrials.gov/show/NCT01849562

69. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01724086, A study to evaluate the safety, tolerability, and effectiveness of a 12-week combination therapy of TMC647055 and TMC435 with and without GSK23336805 with a pharmacokinetic enhancer with and without ribavirin in patients infected with chronic genotype 1 hepatitis C virus; 2014 Oct 9 [cited 2014 Nov 5]. Available from: http://clinicaltrials.gov/show/NCT01724086

70. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01909804, Safety and efficacy of sofosbuvir plus GS-5816 with or without ribavirin in treatment-experienced subjects with chronic HCV infection; 2014 Sep 11 [cited 2014 Nov 5]. Available from: http://clinicaltrials.gov/show/NCT01909804

71. Highleyman L. CROI 2014: short 6-week oral treatment works for most hepatitis C patients [Internet]. San Francisco (CA): HIVandHepatitis.com; 2014 Mar 4. [cited 2015 Apr 7]. Available from: http://www.hivandhepatitis.com/hcv-treatment/experimental-hcv-drugs/4541-croi-2014-short-all-oral-treatment-works-for-many-hard-to-treat-hepatitis-c-patients

72. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02226549, Ledipasvir/sofosbuvir fixed-dose combination and vedroprevir with or without ribavirin in treatment-experienced participants with chronic genotype 1 HCV infection and cirrhosis; 2014 Oct 7 [cited 2014 Nov 5]. Available from: http://clinicaltrials.gov/show/NCT02226549

73. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02133131, Efficacy and safety of MK-5172, MK-8742, and sofosbuvir for chronic infection with hepatitis C virus genotypes 1, 2, and 3 (MK-5172-074); 2014 Nov 4 [cited 2014 Nov 5]. Available from: http://clinicaltrials.gov/show/NCT02133131

74. Lawitz E, Poordad F, Gutierrez JA, Evans B, Hwang P, Robertson M, et al. C-SWIFT: MK-5172 + MK-8742 + sofosbuvir in treatment-naive patients with hepatitis C virus genotype 1 infection, with and without cirrhosis, for durations of 4, 6, or 8 weeks [abstract]. Hepatology. 2014 Oct;60(1 Suppl):LB-33.

75. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02243280, A study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 in subjects with HCV genotype 1 infection; 2014 [cited 2014 Dec 17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02243280

76. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01995071, A study to evaluate the safety and antiviral effect of multiple doses of ABT-493 and ABT-530 in adults with genotype 1 hepatitis C virus (HCV); 2014 Oct 28 [cited 2015 Jan 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT01995071

77. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02032875, Phase III daclatasvir, sofosbuvir, and ribavirin in cirrhotic subjects and subjects post-liver transplant (ALLY 1); 2014 Dec 31 [cited 2015 Jan 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT02032875

78. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT02032888, Phase III HIV/HCV co-infection daclatasvir (DCV) + sofosbuvir (SOF) (ALLY 2); 2014 Dec 31 [cited 2015 Jan 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT02032888

Appendix A

Table A-1: Summary of Phase 2 and 3 Studies of All-Oral Regimens for Genotype 1 Chronic Hepatitis C

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
LDV/SOF (Gilead) (Harvoni)							
Afdhal, 2014[38] ION-1 Phase 3, open-label RCT	865	Treatment-naive patients (≥ 18 years) with HCV genotype 1a (67%) and 1b (33%)	SOF 400 mg and LDV 90 mg (single fixed-dose combination tablet) once daily RBV according to body weight[a]	LDV/SOF for 12 weeks LDV/SOF with RBV for 12 weeks LDV/SOF for 24 weeks LDV/SOF with RBV for 24 weeks	United States Europe	SVR12 LDV/SOF for 12 weeks — 99% (95% CI, 96% to 100%) LDV/SOF with RBV for 12 weeks — 97% (95% CI, 94% to 99%) LDV/SOF for 24 weeks — 98% (95% CI, 95% to 99%) LDV/SOF with RBV for 24 weeks — 99% (95% CI, 97% to 100%) PRO scores related to work, productivity, and fatigue were higher for RBV-free regimens.[58] RBV treatment was associated with decrements in PROs from baseline.[58]	Small number of participants in each treatment arm. Open-label design is a limitation for the assessment of subjective outcomes (PROs). While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Comparison with a historical control is not equivalent to randomizing participants to treatment or control and then making a statistical comparison between groups. Unclear how similar the historical control patients and study participants would be, thereby decreasing confidence in the findings. Unclear whether the treatment received by the historical control aligns with current practice. Thus, the relevance of a comparison to these treatment regimens is unclear.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Afdhal, 2014[35] ION-2 Phase 3, open-label RCT	440	Patients (≥ 18 years) with HCV genotype 1a (79%) and 1b (21%) who did not have an SVR to PR or NS3/4A PI combined with RBV	SOF 400 mg and LDV 90 mg (single fixed-dose combination tablet) once daily RBV according to body weight[a]	LDV/SOF for 12 weeks LDV/SOF with RBV for 12 weeks LDV/SOF for 24 weeks LDV/SOF with RBV for 24 weeks	United States	SVR12 LDV/SOF for 12 weeks — 94% (95% CI, 87% to 97%) LDV/SOF with RBV for 12 weeks — 96% (95% CI, 91% to 99%) LDV/SOF for 24 weeks 99% (95% CI, 95% to 100%) LDV/SOF with RBV for 24 weeks 99% (95% CI, 95% to 100%) SVR24 — all patients with an SVR12 response had an SVR at 24 weeks	Patients who had discontinued prior treatment because of an adverse effect were excluded. This may have led to the selection of patients who would be less likely to have an adverse event. While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Comparison with historical control for primary outcome.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Kowdley, 2014[39] ION-3 Phase 3, open-label RCT	647	Treatment-naive patients (≥ 18 years) with HCV genotype 1a (80%) or 1b (20%) without cirrhosis who had not received treatment previously	SOF 400 mg and LDV 90 mg (single fixed-dose combination tablet) once daily RBV according to body weight[a]	LDV/SOF for 8 weeks LDV/SOF with RBV for 8 weeks LDV/SOF for 12 weeks	United States	SVR12 LDV/SOF for 8 weeks — 94% (95% CI, 90% to 97%) LDV/SOF + RBV for 8 weeks — 93% (95% CI, 89% to 96%) LDV/SOF for 12 weeks — 95% (95% CI, 92% to 98%) LDV/SOF for 8 weeks was non-inferior to the other treatment arms	Patients with cirrhosis were excluded. While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Comparison with historical control for primary outcome.
Lawitz, 2014[36] LONESTAR Phase 2, open-label RCT	100	Treatment-naive, non-cirrhotic patients (≥ 18 years) with HCV genotype 1a (88%) or 1b (12%) (n = 60)	SOF 400 mg and LDV 90 mg (single fixed-dose combination tablet) once daily RBV according to body weight[a]	Treatment-naive LDV/SOF for 8 weeks LDV/SOF with RBV for 8 weeks LDV/SOF for 12 weeks Treatment-experienced LDV/SOF for 12 weeks LDV/SOF with RBV for 12 weeks	United States	SVR12 Treatment-naive LDV/SOF for 8 weeks — 95% (95% CI, 75% to 100%) LDV/SOF with RBV for 8 weeks — 100% (95% CI, 84% to 100%) LDV/SOF for 12 weeks — 95% (95% CI, 74% to 100%)	Patients with coinfection with HIV or hepatitis B were excluded. Patients who discontinued treatment with a PI (with PR) because of a prior adverse effect were excluded. There was a limited number of patients in each treatment arm (19 to 21) and the study was conducted at a single centre, which could limit generalizability.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
		Treatment-experienced patients with HCV genotype 1a (85%) or 1b (15%) (virologic failure with PI) (n = 40)				Treatment-experienced LDV/SOF for 12 weeks — 1% (95% CI, 74% to 100%) LDV/SOF with RBV for 12 weeks — 100% (95% CI, 74% to 100%)	While the assessment of SVR is objective, reporting of adverse events could potentially be biased.
Bourlière, 2014[59] Double-blind, placebo-controlled phase 2 RCT	155	Patients with genotype 1 CHC with compensated cirrhosis who had not previously obtained an SVR with PR and with PR + PI	SOF 400 mg and LDV 90 mg (single fixed-dose combination tablet) once daily RBV according to body weight (dosage not reported)	LDV/SOF for 24 weeks Placebo for 12 weeks, followed by LDV/SOF + RBV for 12 weeks	France	SVR12 LDV/SOF for 24 weeks —97% (CI not reported) LDV/SOF + RBV for 12 weeks — 96% (CI not reported)	Select population, which may limit the generalizability to the broader population with genotype 1 CHC. While the assessment of SVR is objective, reporting of adverse events could potentially be biased.
SOF/RBV (Gilead)							
Osinusi, 2013[41] Phase 2, open-label RCT	50	Treatment-naive patients[b] with HCV genotype 1 Seronegative for HIV and hepatitis B	SOF 400 mg once daily RBV according to body weight[a] RBV 600 mg per day	SOF/RBV according to body weight for 24 weeks[a] SOF/RBV 600 mg per day for 24 weeks	United States	SVR24 SOF/RBV according to body weight — 68% (95% CI, 46% to 85%) SOF/RBV 600 mg — 48% (95% CI, 28% to 69%) (P = 0.20)	Because of the sample size, the investigators indicated that the results should be considered preliminary and that subsequent study is required to determine the optimal dose of RBV. While the assessment of SVR is objective, reporting of adverse events could potentially be biased.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
SOF/LDV and GS-9669 compared with LDV/SOF (both with RBV) (Gilead)							
Gane, 2014[42] ELECTRON Phase 2, open-label RCT	113	Treatment-naive, non-cirrhotic, HCV genotype 1 patients (n = 75) and treatment-experienced, cirrhotic, HCV genotype 1 patients who were non-responders (n = 38) 87% genotype 1a	400 mg SOF and LDV 90 mg (single fixed-dose combination tablet) once daily GS-9669 500 mg once daily RBV according to body weight[a]	Treatment-naive LDV/SOF with RBV for 12 weeks SOF and GS-9669 with RBV for 12 weeks LDV/SOF with RBV for 6 weeks Treatment-experienced LDV/SOF with RBV for 12 weeks SOF and GS-9669 with RBV for 12 weeks LDV/SOF with RBV for 12 weeks (cirrhotic) LDV/SOF for 12 weeks (cirrhotic)	New Zealand	SVR12 Treatment-naive LDV/SOF with RBV for 12 weeks — 100% (95% CI, 86% to 100%) SOF and GS-9669 with RBV for 12 weeks — 100% (92% CI, 74% to 96%) LDV/SOF with RBV for 6 weeks — 68% (95% CI, 47% to 85%) Treatment-experienced LDV/SOF with RBV for 12 weeks — 100% (95% CI, 66% to 100%) SOF and GS-9669 with RBV for 12 weeks — 100% (95% CI, 69% to 100%) LDV/SOF for 12 weeks (cirrhotic) — 70% (95% CI, 35% to 93%) LDV/SOF with RBV for 12 weeks (cirrhotic) — 100% (95% CI, 66% to 100%)	There was a limited number of participants in each arm. While the assessment of SVR is objective, reporting of adverse events could potentially be biased.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
SOF/LDV and GS-9669 compared with LDV/SOF and ribavirin (Gilead)							
Lawitz, 2014[43] (Abstract) Phase 2, open-label RCT	100	Patients with HCV genotype 1 and compensated cirrhosis	Ledipasvir/ sofosbuvir and Ribavirin (doses not reported) GS-9669 250 mg or 500 mg	LDV/SOF + RBV for 8 weeks LDV/SOF + GS-9669 250 mg for 8 weeks LDV/SOF + GS-9669 500 mg for 8 weeks	United States	SVR12 LDV/SOF + RBV for 8 weeks — 89% LDV/SOF + GS-9669 250 mg for 8 weeks — 91% LDV/SOF + GS-9669 500 mg for 8 weeks — 82%	While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Sample size of individual arms was limited.
SOF and DCV with or without RBV (BMS)							
Sulkowski, 2014[37] Phase 2, open-label RCT	167[c]	Patients between the ages of 18 and 70 years, with HCV genotype 1, 2, or 3 without cirrhosis (previously treated or treatment-naive)	SOF 400 mg once daily DCV 60 mg once daily RBV according to body weight[a]	SOF for 7 days, then SOF and DCV for 23 weeks SOF and DCV for 24 weeks SOF and DCV + RBV for 24 weeks SOF and DCV for 12 weeks SOF and DCV + RBV for 12 weeks	United States	SVR12[d] Previously treated SOF for 7 days, then SOF and DCV for 23 weeks — 100% SOF and DCV for 24 weeks — 100% SOF and DCV + RBV for 24 weeks — 100% SOF and DCV for 12 weeks — 100% SOF and DCV + RBV for 12 weeks — 95% Treatment-naive SOF and DCV for 24 weeks — 100% SOF and DCV + RBV for 24 weeks — 95%	Excluded patients who discontinued treatment with telaprevir or boceprevir because of a prior adverse effect and patients with coinfection of HIV or hepatitis B. Number of patients in each arm was limited, ranging from 14 to 41. While the assessment of SVR is objective, reporting of adverse events could potentially be biased.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
						SVR24 Previously treated SOF for 7 days, then SOF and DCV for 23 weeks — 93% SOF and DCV for 24 weeks — 100% SOF and DCV + RBV for 24 weeks — 100% SOF and DCV for 12 weeks — 95% SOF and DCV + RBV for 12 weeks — 93% Treatment-naive Not reported	
SOF and GS-5816 with or without RBV (Gilead)							
Pianko, 2014[45] (Abstract) Phase 2, open-label RCT	321	Treatment-naive patients without cirrhosis with genotype 1 or 3 HCV	SOF 400 mg GS-5816 25 mg or 100 mg RBV 1,000 mg to 1,200 mg daily	SOF and GC-5816 25 mg for 12 weeks SOF and GS-5816 25 mg + RBV for 12 weeks SOF and GC-5816 100 mg for 12 weeks SOF and GS-5816 100 mg + RBV for 12 weeks	Not reported	SVR 12 Genotype 1 with cirrhosis SOF and GS-5816 25 mg for 12 weeks — 100% SOF and GS-5816 25 mg + RBV for 12 weeks — 97%	Relatively small subgroups While the assessment of SVR is objective, reporting of adverse events could potentially be biased.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
						SOF and GC-5816 100 mg for 12 weeks — 100% SOF and GS-5816 100 mg + RBV for 12 weeks — 93%	
Tran, 2014[44] (Abstract) Phase 2, open-label RCT	177 with genotype 1	Treatment-naive patients without cirrhosis with genotype 1 to 6 HCV	SOF 400 mg GS-5816 25 mg or 100 mg RBV 1,000 mg to 1,200 mg daily	SOF and GS-5816 25 mg for 8 weeks SOF and GS-5816 100 mg for 8 weeks SOF and GS-5816 25 mg + RBV for 8 weeks SOF and GS-5816 100 mg + RBV for 8 weeks SOF and GS-5816 25 mg for 12 weeks SOF and GS-5816 100 mg for 12 weeks	Not reported	SVR 12[d] SOF and GC-5816 25 mg for 8 weeks — 87% SOF and GC-5816 100 mg for 8 weeks — 90% SOF and GC-5816 25 mg + RBV for 8 weeks — 83% SOF and GC-5816 100 mg + RBV for 8 weeks — 81% SOF and GC-5816 25 mg for 12 weeks — 96% SOF and GC-5816 100 mg for 12 weeks — 100%	Relatively small subgroups While the assessment of SVR is objective, reporting of adverse events could potentially be biased.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Paritaprevir/RTV/OBV (AbbVie)							
Chayama, 2015[46] Phase 2, randomized, open-label	73	Non-cirrhotic treatment-experienced null or partial responders with HCV genotype 1b aged 18 to 75 years	Paritaprevir/ ritonavir (100 mg/ 100 mg) once daily Paritaprevir/ ritonavir (150 mg/100 mg) once daily OBV 25 mg once daily	OBV 25 mg, paritaprevir/ ritonavir 100 mg/100 mg for 12 weeks OBV 25 mg, paritaprevir/ ritonavir 150 mg/100 mg for 12 weeks OBV 25 mg plus paritaprevir/ ritonavir 100 mg/100 mg for 24 weeks OBV 25 mg, paritaprevir/ ritonavir 150 mg/100 mg for 24 weeks	Japan	SVR12 OBV 25 mg, paritaprevir/ritonavir 100 mg/100 mg for 12 weeks — 100% OBV 25 mg, paritaprevir/ritonavir 150 mg/100 mg for 12 weeks — 89% OBV 25 mg plus paritaprevir/ritonavir 100 mg/100 mg for 24 weeks — 100% OBV 25 mg, paritaprevir/ ritonavir 150 mg/ 100 mg for 24 weeks — 100%	Small sample size in each arm. While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Excluded patients who were treatment-naive, genotype 1a, and those with cirrhosis, coinfection with HIV or hepatitis B Conducted only in Japan, which may limit the generalizability of the findings.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Paritaprevir/RTV/OBV and DSV with and without RBV (AbbVie) (Holkira)							
Andreone, 2014[8] PEARL-II Phase 3, open-label RCT	179	Non-cirrhotic, treatment-experienced patients between the ages of 18 and 70 years with HCV genotype 1b	ABT-450r/ OBV (150 mg/ 100 mg/25 mg) co-formulated tablet once daily DSV 250 mg twice daily RBV according to body weight[a]	ABT-450r, OBV, DSV for 12 weeks ABT-450r, OBV, DSV + RBV for 12 weeks	Europe and the United States	SVR12 ABT-450r, OBV, DSV for 12 weeks — 97% (95% CI, 93% to 100%) ABT-450r, OBV, DSV + RBV for 12 weeks — 100% (95% CI, 96% to 100%) Treatments were found to be non-inferior based on the pre-specified non-inferiority margin of 10.5%.	Excluded patients with coinfection with HIV or hepatitis B, genotype 1a. While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Comparison with historical control for primary outcome.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Ferenci, 2014[9] PEARL-III and PEARL-IV Phase 3, double-blind RCTs	PEARL-III — 419 PEARL-IV — 305	Non-cirrhotic, treatment-naive patients between the ages of 18 and 70 years with HCV genotype 1b (PEARL-III) Non-cirrhotic, treatment-naive patients between the ages of 18 and 70 years with HCV genotype 1a (PEARL-IV)	ABT-450r/ OBV (150 mg/ 100 mg/25 mg) co-formulated tablet once daily DSV 250 mg twice daily RBV according to body weight[a]	PEARL-III — Genotype 1b ABT-450r, OBV, DSV for 12 weeks ABT-450r, OBV, DSV + RBV for 12 weeks PEARL-IV — Genotype 1a ABT-450r, OBV, DSV for 12 weeks ABT-450r, OBV, DSV + RBV for 12 weeks	PEARL-III Europe and the United States PEARL-IV Canada, United States, United Kingdom	PEARL-III SVR12 ABT-450r, OBV, DSV for 12 weeks — 90% (95% CI, 86% to 94%) ABT-450r, OBV, DSV + RBV for 12 weeks — 97% (95% CI, 94% to 100%) Non-inferiority was not found based upon a pre-specified non-inferiority margin of 10.5%. PEARL-IV SVR12 ABT-450r, OBV, DSV for 12 weeks — 99% (95% CI, 98% to 100%) ABT-450r, OBV, DSV + RBV for 12 weeks — 99.5% (95% CI, 99% to 100%) Treatments were found to be non-inferior based on the pre-specified non-inferiority margin of 10.5%.	Excluded patients with coinfection with HIV or hepatitis B. While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Comparison with historical control for primary outcome.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Feld, 2014[10] SAPPHIRE-I Phase 3, double-blind, placebo-controlled RCT	631	Non-cirrhotic, treatment- naive patients between the ages of 18 and 70 years with HCV genotype 1a (68%) or 1b (32%)	ABT-450r/ OBV (150 mg/ 100 mg/25 mg) co-formulated tablet once daily DSV 250 mg twice daily RBV according to body weight[a]	ABT-450r, OBV, DSV + RBV for 12 weeks Placebo for 12 weeks	North America, Australia, Europe	SVR12 ABT-450r, OBV, DSV + RBV for 12 weeks — 96% (95% CI, 95% to 98%) Non-inferior to a historical control rate. Placebo for 12 weeks — not reported	Excluded patients with HIV and hepatitis B, uncontrolled seizures or diabetes, active or suspected malignancy, those with a recent history of drug or alcohol abuse and evidence of current or past cirrhosis. Comparison with historical control for primary outcome.
Zeuzem, 2014[11] SAPPHIRE-II Phase 3, double-blind, placebo-controlled RCT	394	Non-cirrhotic, treatment-experienced patients between the ages of 18 and 70 years with HCV genotype 1a (59%) or 1b (41%)	ABT-450r/ OBV (150 mg/ 100 mg/25 mg) co-formulated tablet once daily DSV 250 mg twice daily RBV according to body weight[a]	ABT-450r, OBV, DSV + RBV for 12 weeks Placebo for 12 weeks	North America, Australia, Europe	SVR12 ABT-450r, OBV, DSV + RBV for 12 weeks — 96% (95% CI, 94% to 98%) Non-inferior and superior to a historical control rate Placebo for 12 weeks — not reported	Excluded patients with HIV and hepatitis B; patients using contraindicated medications; patients who failed to respond to a PI, RBV, and interferon triple therapy; patients with advanced-stage cirrhosis; and patients with a recent history of drug or alcohol abuse. Comparison with historical control for primary outcome.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Kowdley, 2014[47] AVIATOR Phase 2b, open-label RCT	571	Treatment-naive and treatment-experienced patients (aged 18 to 70 years) with HCV genotype 1a and 1b Treatment-naive, genotype 1a (68%) Treatment-experienced, genotype 1a (61%)	ABT-450 100 mg, 150 mg, or 200 mg daily with ritonavir 100 mg daily OBV 25 mg daily DSV 400 mg twice daily RBV according to body weight[a]	Treatment-naive ABT-450r 150 mg DSV, OBV + RBV for 8 weeks ABT-450r 150 mg, DSV + RBV for 12 weeks ABT-450r 100 mg, OBV, + RBV for 12 weeks	Canada, United States, Australia, Europe, Puerto Rico, New Zealand	SVR24 Treatment-naive ABT-450r 150 mg, DSV, OBV + RBV for 8 weeks — 87.5% (95% CI, 78% to 94%) ABT-450r 150 mg, DSV + RBV for 12 weeks — 82.9% (95% CI, 68% to 93%) ABT-450r 100 mg, OBV, + RBV for 12 weeks — 84.6% (95% CI, 69% to 94%)	While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Small sample size in each arm. Exclusion of patients with cirrhosis, who tend to be less likely to respond to treatment.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
				ABT-450r 200 mg, OBV, + RBV for 12 weeks ABT-450r 150 mg, DSV, OBV for 12 weeks ABT-450r 100 mg, DSV, OBV + RBV for 12 weeks ABT-450r 150 mg, DSV, OBV + RBV for 12 weeks ABT-450r 100 mg, DSV, OBV + RBV for 24 weeks ABT-450r 150 mg, DSV, OBV + RBV for 24 weeks Treatment-experienced ABT-450r 200 mg, OBV, + RBV for 12 weeks ABT-450r 100 mg, DSV, OBV + RBV for 12 weeks		ABT-450r 200 mg, OBV, + RBV for 12 weeks — 92.5% (95% CI, 80% to 98%) ABT-450r 150 mg, DSV, OBV for 12 weeks — 88.6% (95% CI, 79% to 95%) ABT-450r 100 mg, DSV, OBV + RBV for 12 weeks — 97.4% (95% CI, 87% to 100%) ABT-450r 150 mg, DSV, OBV + RBV for 12 weeks — 95.0% (95% CI, 83% to 99%) ABT-450r 100 mg, DSV, OBV + RBV for 24 weeks — 92.5% (95% CI, 80% to 98%) ABT-450r 150 mg, DSV, OBV + RBV for 24 weeks — 90.0% (95% CI, 76% to 97%)	

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
DCV and ASV (BMS)							
Manns, 2014[48] HALLMARK DUAL Phase 3 RCT (placebo-controlled for treatment-naive)	307 treatment-naive patients 205 previous non-responders to PR 235 ineligible for or intolerant to PR	Treatment-naive patients with HCV genotype 1b, with or without cirrhosis	DCV 60 mg once daily ASV 100 mg twice daily Placebo	Treatment-naive DCV + ASV for 12 weeks in double-blind phase (followed by additional 12 weeks of open-label treatment) Placebo for 12 weeks Non-responders DCV + ASV for 24 weeks Ineligible for/ intolerant to DCV + ASV for 24 weeks	North America, Europe, Asia, South America	SVR12 Treatment-naive DCV + ASV for 24 weeks —90% (95% CI, 85% to 94%) Placebo for 12 weeks Not reported Non-responders DCV + ASV for 24 weeks —82% (95% CI, 77% to 87%) Ineligible for/intolerant to DCV + ASV for 24 weeks —82% (95% CI, 77% to 87%)	No comparator for non-responders and ineligible/ intolerant cohort No comparison between the placebo and DCV + ASV groups for treatment-naive patients SVR12 not reported for placebo group While the assessment of SVR is objective, reporting of adverse events could potentially be biased for the non-responder and ineligible/intolerant groups.
DCV, ASV, and BCV with or without RBV (BMS)							
Muir, 2014[20] (Abstract) UNITY-2 Phase 3 RCT, blinded to RBV therapy	112 treatment-naive 90 treatment-experienced	Treatment-naive and treatment-experienced patients with HCV genotype (GT) 1 infection and compensated cirrhosis	DCV 30 mg ASV 200 mg BCV 75 mg Blinded RBV or placebo All administered twice daily	DCV, ASV, and BCV + placebo for 12 weeks DCV, ASV and BCV + RBV for 12 weeks	Reported as international	SVR12 Treatment-naive DCV, ASV, and BCV + placebo for 12 weeks — 93% DCV, ASV, and BCV + RBV for 12 weeks — 98%	While the assessment of SVR is objective, reporting of adverse events could potentially be biased. It is important to assess efficacy in patients with cirrhosis, but it is unclear whether results would be generalizable to patients without cirrhosis.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
						Treatment-experienced DCV, ASV, and BCV + placebo for 12 weeks — 87% DCV, ASV, and BCV + RBV for 12 weeks — 93%	
Grazoprevir/elbasvir with or without RBV (Merck)							
Sulkowski, 2014[49] C-WORTHY study Part B Phase 2, open-label RCT	159 HCV mono-infected patients 59 HIV/HCV coinfected	Treatment-naive, non-cirrhotic genotype 1 HCV Monoinfected and HIV/HCV-coinfected patients	Grazoprevir 100 mg once daily Elbasvir 20 mg or 50 mg once daily Weight-based RBV: 51 to 65 kg, 800 mg; 66 to 80 kg, 1,000 mg; 81 to 105 kg, 1,200 mg; and > 105 kg to 125 kg, 1,400 mg	Monoinfected Grazoprevir/elbasvir + RBV for 8 weeks Grazoprevir/elbasvir + RBV for 12 weeks Grazoprevir/elbasvir for 12 weeks Coinfected Grazoprevir/elbasvir + RBV for 12 weeks Grazoprevir/elbasvir for 12 weeks	International	SVR12 Monoinfected Grazoprevir/elbasvir + RBV for 8 weeks — 80% (95% CI, 61% to 92%) Grazoprevir/elbasvir + RBV for 12 weeks — 93% (95% CI, 85% to 97%) Grazoprevir/elbasvir for 12 weeks — 98% (95% CI, 88% to 100%) Coinfected Grazoprevir/elbasvir + RBV for 12 weeks — 97% (95% CI, 82% to 100%) Grazoprevir/elbasvir for 12 weeks — 87% (95% CI, 69% to 96%)	Small treatment arms, particularly those with coinfected patients. While the assessment of SVR is objective, reporting of adverse events could potentially be biased. Patients with cirrhosis were excluded. There were restrictions on the permissible antiretroviral regimens.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
Lawitz, 2014[50] C-WORTHY study Part B Phase 2, open-label RCT	123 previously untreated patients with cirrhosis 130 null responders with or without cirrhosis	Previously untreated patients with cirrhosis and those with previous PR-null response with or without cirrhosis with genotype 1 HCV	Grazoprevir 100 mg once daily Elbasvir 20 mg or 50 mg once daily Weight-based RBV: 51 to 65 kg, 800 mg; 66 to 80 kg, 1,000 mg; 81 to 105 kg, 1,200 mg; and > 105 kg to 125 kg, 1,400 mg	Previously treated, with cirrhosis Grazoprevir/elbasvir + RBV for 12 weeks Grazoprevir/elbasvir for 12 weeks Grazoprevir/elbasvir + RBV for 18 weeks Grazoprevir/elbasvir for 18 weeks Null responders Grazoprevir/elbasvir + RBV for 12 weeks Grazoprevir/elbasvir for 12 weeks Grazoprevir/elbasvir + RBV for 18 weeks Grazoprevir/elbasvir for 18 weeks	International	SVR12 Previously treated, with cirrhosis Grazoprevir/elbasvir + RBV for 12 weeks — 90% (95% CI, 74% to 98%) Grazoprevir/elbasvir for 12 weeks — 97% (95% CI, 82% to 100%) Grazoprevir/elbasvir + RBV for 18 weeks — 97% (95% CI, 84% to 100%)	Relatively small treatment arms While the assessment of SVR is objective, reporting of adverse events could potentially be biased. The patients with cirrhosis were well compensated. It is unclear whether the results would be generalizable to those patients with decompensated cirrhosis. Patients who were medically fragile were excluded.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
						Grazoprevir/elbasvir for 18 weeks — 94% (95% CI, 79% to 99%) Null responders Grazoprevir/elbasvir + RBV for 12 weeks — 94% (95% CI, 79% to 99%) Grazoprevir/elbasvir for 12 weeks — 91% (95% CI, 76% to 98%) Grazoprevir/elbasvir + RBV for 18 weeks — 100% (95% CI, 89% to 100%) Grazoprevir/elbasvir for 18 weeks — 97% (95% CI, 84% to 100%)	

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
DCV and SMV with or without RBV (Janssen and BMS)							
Zeuzem, 2014[51] LEAGUE-1 study (Abstract) Phase 2, open-label RCT	104 treatment-naive and 43 treatment-experienced (null responders)	Treatment-naive or treatment-experienced patients with HCV genotype 1 (21% cirrhotic)	DCV 30 mg SMV 150 mg RBV according to body weight (dosing not reported)	DCV and SMV for 12 weeks DCV and SMV + RBV for 12 weeks DCV and SMV for 24 weeks DCV and SMV + RBV for 24 weeks	Not reported	Genotype 1b Naive (12 weeks of treatment) DCV/SMV — 81% DCV/SMV + RBV — 75% Genotype 1b Naive (24 weeks of treatment) DCV/SMV — 89% DCV/SMV + RBV — 74% Genotype 1b Null-responder (12 weeks of treatment) DCV/SMV — 83% DCV/SMV + RBV — 100%	Small number of patients in genotype 1a arms (12 and 9). Dose of DCV was lower than that currently being used in ongoing studies of the DCV/SMV combination and other DCV-containing regimens. This may limit the generalizability of the findings. While the assessment of SVR is objective, reporting of adverse events could potentially be biased.

Author, Year, Study Name, Design	N	Population	Study Drugs	Treatment Arms	Study Location	Outcomes, Study Follow-Up	Limitations
						Genotype 1b Null-responder (24 weeks of treatment) DCV/SMV — 50% DCV/SMV + RBV — 89% Genotype 1a (24 weeks of treatment) Naive DCV/SMV + RBV — 67% Genotype 1a (24 weeks of treatment) Null DCV/SMV + RBV — 0%	

ASV = asunaprevir; BCV = beclabuvir; CHC = chronic hepatitis C; CI = confidence interval; DCV = daclatasvir; DSV = dasabuvir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDV = ledipasvir; OBV = ombitasvir; PI = protease inhibitor; PR = pegylated interferon and ribavirin; PRO = patient-reported outcome; r = ritonavir; RBV = ribavirin; RCT = randomized controlled trial; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; SVR12 = sustained virologic response at 12 weeks; SVR24 = sustained virologic response at 24 weeks;

[a] 1,000 mg for weight < 75 kg or 1,200 mg for weight ≥ 75 kg.

[b] Age not specified as an inclusion criterion, but all patients were adults.

[c] Patients with HCV type 2 or 3 were also included, in addition to the 167 with genotype 1.

[d] 95% CIs not reported.

Appendix B

Table B-1: All-Oral Regimens for Genotype 1 Chronic Hepatitis C in Phase 2 or Phase 3 Trials Without Published Results

Regimen	Study Phase	Population
Simeprevir and sofosbuvir	Phase 4[60]	Genotype 1 CHC patients with compensated cirrhosis Comparison of PR and sofosbuvir with the off-label combination of simeprevir and sofosbuvir
Simeprevir, sofosbuvir, and daclatasvir	Phase 2[61,62]	Patients with decompensated liver disease due to genotype 1 or 4 CHC Treatment-naive patients with genotype 1 CHC with early stages of liver fibrosis or with cirrhosis
Simeprevir and sofosbuvir with or without ribavirin	Phase 2[63]	Post-orthotopic liver transplant participants with recurrent genotype 1 CHC
Samatasvir and simeprevir	Phase 2[64]	Treatment-naive or interferon/RBV treatment-relapsed patients with genotype 1 CHC
Simeprevir and daclatasvir	Phase 2[65]	Patients with genotype 1b CHC who are treatment-naive and have advanced fibrosis or compensated cirrhosis
Simeprevir, daclatasvir, and ribavirin	Phase 2[66]	Patients with genotype 1b CHC post-orthotopic liver transplantation
Samatasvir, simeprevir, and/or TMC647055/ritonavir, with or without ribavirin	Phase 2[64,67]	Genotype 1a, 1b, 4, or 6 HCV infection HCV treatment-naive or interferon/RBV treatment-relapsed
Sovaprevir, ACH-3102, and ribavirin	Phase 2[68]	Treatment-naive patients with genotype 1 CHC
TMC647055/ritonavir, simeprevir, GSK23336805, with or without ribavirin	Phase 2[69]	Treatment-naive genotype 1 CHC patients or patients with a documented prior relapse to previous treatment regimens
Sofosbuvir and GS-5816, with or without ribavirin	Phase 2[70]	Treatment-experienced patients with CHC genotype 1 or 3
Ledipasvir/sofosbuvir and vedroprevir (GS-9451) or GS-9669, with or without ribavirin[71]	Phase 2[72]	Treatment-experienced adults with genotype 1 CHC and cirrhosis
Grazoprevir/elbasvir and sofosbuvir	Phase 2[73] Phase 2[74] (C-SWIFT study)	Treatment-naive patients with genotype 1, 2, or 3 CHC Treatment-naive cirrhotic and non-cirrhotic patients with genotype 1, 2, or 3 CHC
ABT-530, ABT-493	Phase 2[75]	Treatment-naive patients or null responders, without cirrhosis
Paritaprevir/ritonavir, dasabuvir, ombitasvir, ABT-493, ABT-530	Phase 2[76]	Adults with genotype 1 CHC
Sofosbuvir and daclatasvir	Phase 3[77,78]	Patients with genotype 1 to 6 CHC with cirrhosis who may require future liver transplant and patients post-liver transplant.

CHC = chronic hepatitis C; HCV = hepatitis C virus; PR = pegylated interferon and ribavirin; RBV = ribavirin.