An Update: Management and Treatment of Hepatitis C Virus Infection

Geri Brown MD

Department of Internal Medicine

September 5, 2014

Conflict of Interest: This is to acknowledge that Geri Brown, M.D. has disclosed that she does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Brown will be discussing off-label uses in his/her presentation

Biographical Information

Geri Brown MD is Professor of Internal Medicine (Division of Digestive and Liver Diseases) at the University of Texas Southwestern Medical Center. She graduated from University of Texas Southwestern Medical School and completed her internal medicine residency and fellowship at UT Southwestern Medical Center. She has been active in seeing patients with liver disease at the VA North Texas Healthcare System. Her interests include management and care of patients with chronic hepatitis C viral infection as well as the care of patients with complications of cirrhosis. She has been involved in clinical trials of patients with hepatitis C, ranging from the use of interferon based therapies to the use of all-oral direct acting antiviral agents.

Purpose and Overview –

The purpose of this presentation is to provide an update of the management and treatment of hepatitis C. The presentation provides an overview of the guidelines for screening for hepatitis C and the recommended hepatitis C education and interventions. In the next section of the presentation, the clinical trials that led to the current practice guidelines are reviewed. Finally, select investigational medications in late phase clinical development are reviewed.

Educational Objectives

1. Understand the guidelines regarding screening for chronic hepatitis C viral infection

2.Understand the recommended education and interventions for chronic hepatitis C viral infection

3.Understand the clinical trials that led to the current practice guidelines

4.Understand the clinical trials regarding select investigational medications in late phase clinical development.

BACKGROUND

The hepatitis C virus (HCV) with an estimated 180 million people infected worldwide is a leading cause of chronic liver disease (1, 2). There is an estimated 2.7 million to 3.9 million persons (1999 to 2008 National Health and Nutrition Examination Survey data (3) chronically infected with HCV in the United States. Approximately 80% of acutely infected HCV patients progress to chronic infection, 20% of whom develop cirrhosis within 25 years. Approximately 25% of patients with cirrhosis develop hepatocellular carcinoma and/or decompensated liver disease (4, 5).

HCV Education/Intervention

In 2014, a national task force, which included members of both the American Association for the Study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA) provided a comprehensive set of guidelines for clinicians with regard to management of patients infected with the chronic hepatitis C virus (6). Regarding screening, HCV testing was recommended in select populations based on demography, prior exposures, high-risk behaviors, and medical conditions. Specifically, the guidelines recommended annual HCV testing for persons who inject drugs, HIV seropositive men who have unprotected sex with men and ongoing risk factors. Furthermore, one time testing was recommended for the cohort of asymptomatic adults born between 1945 through 1965, as well as persons with conditions associated with a high prevalence, including patients on hemodialysis, those persons with abnormal aminotransferases, recipients of transfusions/organ transplants before 1992 or clotting factor concentrates before 1987, children born to HCV-infected mothers and those persons with tatoos or prior episodes of incarceration (6).

For those patients who had positive HCV antibodies, it was recommended for the patients to have a quantitative HCV RNA and HCV genotype prior to initiation of antiviral therapy in order to guide antiviral regimen. Furthermore, the patients should receive education and interventions aimed at reducing progression of liver disease and prevention of the transmission of HCV. Specifically, the patients should be guided regarding alcohol abstinence, treatment of conditions that may accelerate liver fibrosis, including HBV and HIV. All patients prior to treatment should have an assessment for advanced fibrosis either by liver biopsy, imaging or noninvasive markers as well as receive vaccinations against hepatitis A and hepatitis B. The patient should have an evaluation by a practioner who is prepared to provide comprehensive management, including consideration of antiviral therapy (6).

HCV Virus

HCV is a small, enveloped, single-stranded RNA virus. At least 6 major genotypes have been identified (7). The hepatitis C virus consists of both mature structural and nonstructural proteins. The nonstructural proteins are processed by the two viral proteases, the NS2-3 protease and the NS3-4 serine protease. The viral proteins include the, core, the envelope glycoproteins E1 and E2, the protease assembly NS3/NS4A complex, the NS5A RNA replication assembly and the RNA dependent RNA polymerase (8). Each of these proteins are required for active replication of the virus. Viral replication is a multistep process involving viral entry into the cell, followed by release of positive strand of RNA. The RNA is translated into viral proteins, which is followed by polyprotein processing and RNA replication, which involves a RNA dependent RNA polymerase followed by assembly of viral particle and release (9). These enzymatic sites which are required for viral replication provide excellent targets for drug therapies.

DIRECT ACTING ANTIVIRAL AGENTS

For patients with chronic hepatitis C, there are a large number of new direct acting antiviral agents, which target specific hepatitis C virus (HCV) enzymes. Specific steps in the viral replication have become targets for antiviral drug therapies (Table 1). Direct acting antiviral agents disrupt hepatitis C virus (HCV) replication by disrupting critical enzymatic steps in the HCV life cycle.

Table 1

Direct Acting Antiviral Agents for Chronic Hepatitis C

Mode of action	**Mode of Action**
Protease Inhibitor NS3/4aSerine protease inhibitor	**NS5A Replication Complex Inhibitor**
Tela**previr**	Ledip**asvir**
Boce**previr**	Daclat**asvir**
Sime**previr**	Ombit**asvir**
Asuna**previr**	
ABT 450-r	
NS5B Nucleotide Polymerase Inhibitor	**NS5B Non nucleotide Polymerase Inhibitor**
Sofos**buvir**	Dasu**buvir**

Protease Inhibitors

The HCV protease enzyme is a serine proteinase with a catalytic site, two substrate binding sites, an NS4A-binding site and an NS2/NS3 proteinase substrate recognition site, a helicase single strand RNA binding site and a zinc binding site (10, 11). This sites offers multiple potential avenues to inhibit the enzyme and block HCV RNA processing. In general, the protease inhibitors block the translation and polyprotein processing by inhibiting this HCV protease enzyme.

The early FDA protease inhibitors, telaprevir and boceprevir increased sustained virological response when used in combination with interferon/ribavirin based therapy (2). However, these agents have been replaced by more effective protease inhibitors and are not currently recommended

The 2014 AASLD/IDSA guidelines support the use of the FDA approved simeprevir. Other protease inhibitors including asunaprevir and ABT 450-r (r-ritonavir) are undergoing final stages of approval. In this protocol, trials involving the FDA approved simeprevir as well as the protease inhibitors in late phase clinical development, asunaprevir and ABT450-r will be reviewed

In general, protease inhibitors have limitations (often genotype specific, not useful as monotherapies, secondary to rapid emergence of resistance, potential side effects and drug-drug interactions) (10).

Simeprevir (Olysio - trade name))

Simeprevir is a HCV serine protease inhibitor which directly affects a protein, which is required for cleavage of the viral proteins, which is in turn, is essential for viral replication (12). Simeprevir (150 mg tablet daily) is active against HCV genotype 1. Simeprevir is an inhibitor of CYP1A2 activity, intestinal CYP3A4, OATP1B1/B3 and MRP2 as well as p-glycoprotein (13). Simeprevir is expected to have multiple drug interactions because of its effects on these

enzymes. Depending upon the clinic practice settings, medications such as the "statins" and phosphodiesterase inhibitors may require dose changes. The side effects of simeprevir include photosensitivity and hyperbilirubinemia (13).

Asunaprevir (Sunvepra-trade name)

Asunaprevir (100 mg twice daily) is an inhibitor of the HCV nonstructural 3 protease and has been shown to be active against HCV genotype 1 and 4 (14). Similar to other protease inhibitors, there is a low barrier to resistance. Asunaprevir has been used successfully in combination with daclatasvir (NS5A inhibitor). Asunaprevir is an inhibitor of CYP-2D6, weak inducer of CYP - 3A4 activity and a weak inhibitor of OATP-1B1/2B1 as well a p-glycoprotein (13). Similar to previous protease inhibitors, asunaprevir is expected to have multiple drug interactions because of its effects on these enzymes. When used in clinical trials in combination with daclatasvir, side effects included transient increases in aminotransferase levels, nasopharyngitis, headaches, diarrhea and pyrexia.

ABT-450-ritonavir

ABT-450-boosted with ritonavir (r) is a coformulated medication (ABT 450 150mg/ ritonavir100 mg daily) used with dasabuvir (NS5B polymerase inhibitor) and ombitasvir (NS5A inhibitor). This co-formulated medication (ABT450/ritonavir) is an inhibitor of CYP3A4 and OATP1B1 and is expected to have multiple drug interactions (13). Regarding side effects, increased transaminases have been reported in clinical trials.

Polymerase Inhibitors

The NS5B enzyme is a highly conserved structure across all hepatitis C genotypes. The NS5B protein is a RNA-dependent RNA polymerase critical for the viral reproduction cycle making it an ideal target for drug therapy. There are two classes of polymerase inhibitors, nucleotide RNA dependent RNA polymerase analogue inhibitors and non-nucleoside RNA dependent RNA polymerase inhibitors. The nucleotide analogue inhibitors target the catalytic sites of the enzyme, binding to the NS5B active site and act as chain terminators. This mode of action makes variants less fit and unable to replicate, thus proving a high barrier to antiviral resistance. Non-nucleoside inhibitors bind to an allosteric binding pocket outside the active site. Binding of the NNIs to an allosteric binding pocket results in a conformational change in the active site, thereby inhibiting RNA polymerase activity (15)

NS5B Nucelotide Polymerase Inhibitors

Sofosbuvir (Sovaldi) (PSI7977)

Sofosbuvir (400 mg daily) is a prodrug (metabolized to an active antiviral agent) of a nucleotide analogue, which inhibits the HCV NS5B RNA-dependent RNA polymerase. Sofosbuvir serves as a defective substrate for the NS5B protein, which is the viral RNA polymerase, and thus acts as an inhibitor of viral RNA synthesis. Importantly, the drug design team of sofosbuvir built in the first phosphate group into the structure of the drug. By masking the phosphate group, the drug design team facilitated entry of the drug into the infected cell, and enhanced the quicker conversion to the active drug (13, 16-17). Though sofosbuvir is a substrate for p-glycoprotein, there are few significant drug-drug interactions. The side effects that have been reported include insomnia and gastrointestinal complaints.

NS5B Non- Nucleoside Polymerase Inhibitor

Dasabuvir (ABT-333)

Dasabuvir (250 mg twice daily) is a non-nucleoside polymerase inhibitor that binds to different allosteric enzyme sites, resulting in a conformational protein change before the elongation

complex is formed. Dasabuvir has been used in combination with ombitasvir (NS5A inhibitor), the ABT450 protease inhibitor (boosted with ritonavir), with and without ribavirin in both naïve and previously experienced hepatitis C treatment (15,18,19). Dasabuvir is an inhibitor of OATP1B1/B3, BRCP, and is metabolized by CYP-2C8, -2D6 and -3A4 (13). Multiple drug interactions are expected because of its effects on these enzymes. Regarding side effects, increased bilirubin and transaminases have been noted in combination with ABT450-ritonavir/ombitasvir and ribavirin.

NS 5A Replication Complex Inhibitor

There are a number of NS5A replication complex inhibitors. These inhibitors include ledipasvir, daclatasvir and ombitasvir. Ledipasvir (GS-5885) (90 mg daily) has been used in genotype 1 with sofosbuvir (400 mg daily) and demonstrated excellent efficacy. Ledipasvir is not a CYP inhibitor or inducer. However Ledipasvir is a weak inhibitor of OAT-P1B1, OAT-P1B3, BCRP and p-glycoprotein (13, 20). Daclatasvir (BMS 790052) (60 mg daily) has been successfully used in HCV genotype 1-3 in combination with sofosbuvir. This DAA is metabolized by CYP3A4 and has noted to have drug-drug interactions with PPI and midazolam in clinical trials (13,21). Ombitasvir (ABT 267) is a pan-genotypic HCV NS5a replication complex inhibitor against GT1-6 and has been successfully used in combination with the protease inhibitor boosted with ritonavir (r) (ABT-450/r) and an NS5B non-nucleoside polymerase inhibitor (Dasabuvir). Side effects are reported in clinical trials when used with ABT450-R and ombitasvir (13, 22).
The table in appendix 1 summarizes drug-drug interaction potential of currently approved and investigational DAA in late phase clinical development (13) (Appendix 1).

CURRENT CLINICAL TRIALS

Data on interferon and oral interferon-free treatment regimens for patients infected with HCV from clinical trials of US Food and Drug Administration (FDA)–approved medications and select investigational medications in late phase clinical development will be summarized. Prior to the review of the clinical trials, specific terminology will be reviewed.
With regards to the patient population, the trials report outcomes as the sustained virological response by patient cohorts depending upon whether they had been previously treated. Those patients not previously treated are designated as treatment naïve or previously untreated. For those patients, who have received medications, their sensitivity to previous treatment may predict responsiveness to current and future therapy. The following terminology is used throughout the trials: null responders are persons whose HCV RNA level did not decline by at least 2 log IU/ml at treatment week 12 when treated with pegylated interferon and ribavirin based therapy. Non responders are persons who fail to clear HCV RNA after 24 weeks of therapy of pegylated interferon and ribavirin based therapy. Partial responders are persons whose HCV RNA level dropped by at least 2 log IU/ml at treatment week 12 but whom HCV RNA was still detected at treatment week 24. Relapsers are persons whose HCV RNA became undetected during treatment but then reappeared (2).
Many of the current FDA approved regimens for patients with chronic hepatitis C viral infection, genotype (GT) 1-6 include sofosbuvir (SOF) as the backbone medication of the regimen (Table 2). The first 2 regimens, which include pegylated interferon (PEG) and ribavirin (RBV) have been both FDA approved and recommended by national societies. The last 3 regimens, which are all oral combination therapies are currently being reviewed.

Table 2
Combination Direct Acting Antiviral Agents (DAA)

DAA	Clinical Trial	Combination	GT	AASLD/IDSA recommend	FDA approval
NS5B nucleoside polymerase inhibitor					
Sofosbuvir	**NEUTRINO**	**PEG/RBV**	**GT1/4-6**	**Yes**	**Yes**
	FISSION/FUSION	**RBV**	**GT2/3**	**Yes**	**Yes**
	COSMOS	**Simeprevir**	**GT1**	**Yes**	**No**
	ION	**Ledipasvir**	**GT1**	**No**	**No**
	ALLY	**Daclatasvir**	**GT1/2/3**	**No**	**No**

INITIAL CLINICAL TRIALS

Sofosbuvir/PEG/RBV for Genotypes 1 and 4-6 (Treatment Naïve) (NEUTRINO)

One of the initial trials to assess the effect of the NS5B nucleotide polymerase inhibitor was the NEUTRINO trial in patients with genotype (GT) 1 and 4-6 chronic hepatitis C viral infection. The phase 3 NEUTRINO trial evaluated sofosbuvir (400 mg daily) in combination with Pegylated interferon IFNα-2a (180 μg by subcutaneous injection weekly) and weight-based RBV (1000 mg to 1200 mg daily) for 12 weeks in 327 treatment-naive patients. Of note, 17% of the patients had cirrhosis. The overall sustained virological response at 12 weeks (SVR12) for patients with genotype 1 infection was 90% with a SVR12 rate of 92% for GT1a and 82% for GT1b. SVR12 did not differ substantially by baseline characteristic but was lower in patients with cirrhosis (80%) than in those without cirrhosis (92%). Of note, there was no benefit to extending treatment duration to 24 weeks or using response-guided therapy (SVR12 range 89-91% (4, 23, 24) (Figure 1).

Sofosbuvir/RBV (Genotype 2 and 3) (Treatment Naïve) (FISSION)

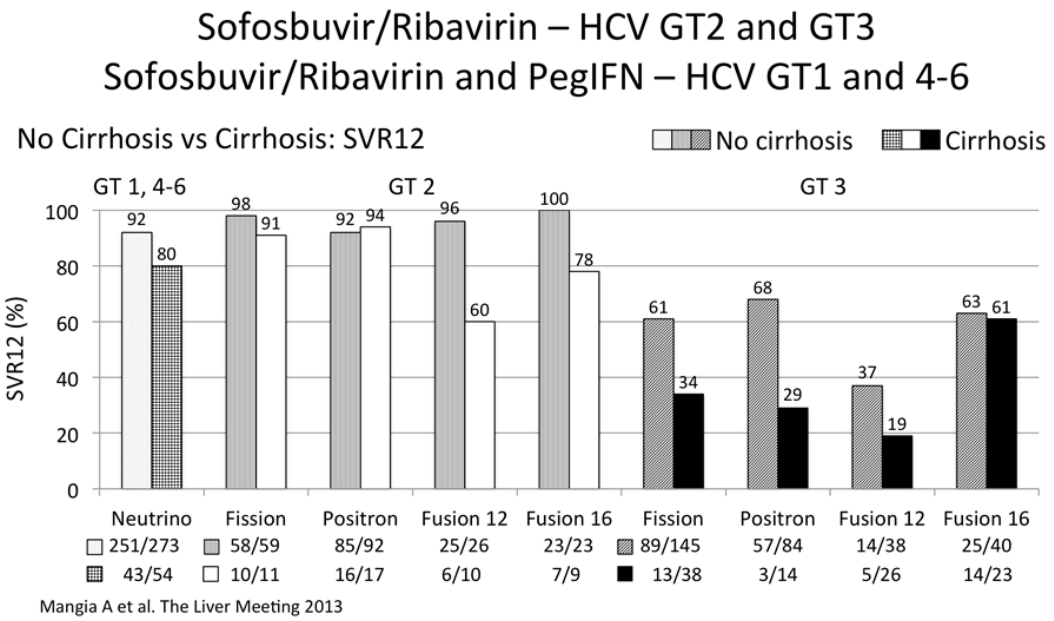
There were a number of trials to assess all oral therapy with sofosbuvir (SOF) and ribavirin (RBV) in patients with genotype 2 and 3 chronic hepatitis C viral infection. The phase 3 FISSION trial was a phase 3 double blinded, randomized control trial with two arms comparing SOF (400 mg daily) in combination with weight based RBV for 12 weeks versus 24 weeks of PEG plus weight based RBV in 527 untreated chronic HCV genotype 2 and 3 patients. In patients with genotype 2 or 3 chronic HCV who received the all oral therapy of SOF/RBV or received the standard therapy of PEG/RBV, a similar SVR12 of 67% was noted. This trial indicated that both GT 2 and 3 could be treated with interferon free regimen (24) (Figure 1).

(FUSION/POSITRON) (Treatment Experienced)

The phase 3 FUSION trial evaluated SOF in combination with weight based RBV for 12 weeks versus 16 weeks in 97 and 103 chronic HCV genotype 2 (~35%) and genotype 3 patients (~ 65%), respectively, with 75% of the patients being relapsers to PEG/RBV based therapy. In patients with genotype 2, SVR12 was 86% and 94% respectively after 12 and 16 weeks of SOF/RBV based therapy. While in chronic HCV genotype 3 patients, SVR12 was 30% and 62% respectively after 12 and 16 weeks of SOF/RBV. In treatment experienced chronic HCV

genotype 2 patients with cirrhosis, SVR12 was 31% and 66% after 12 and 16 weeks while in chronic HCV GT 3 patients, SVR12 was 19 and 61% after 12 and 16 weeks of therapy (25) (Figure 1). The Phase 3 POSITRON trial evaluated SOF in combination with weight based RBV in 207 HCV genotype 2 (~53%) and 3 (~ 47%) patients (all with contraindications to pegylated interferon). In patients with chronic HCV GT 2 and 3 infection, SVR12 was 93% and 61% respectively. In patients with cirrhosis, overall SVR12 was 92% and 21% in GT 2 and 3 respectively after 12 weeks of therapy (25) (Figure 1) .

Figure 1



Simeprevir /PEG/RBV- Genotype 1 (Treatment Naïve and Experienced) (QUEST/PROMISE)

The direct acting antiviral agent (DAA), simeprevir (SMV) was approved for treatment of chronic HCV infection. Simeprevir, an HCV NS3/4 serine protease inhibitor, was initially evaluated in studies for both treatment-naive patients and treatment experienced patients who had relapsed showing higher rates of SVR (75%-86%) using 12 to 24 weeks of simeprevir and 24 to 48 weeks of pegylated interferon + weight based ribavirin compared to standard PEG/RBV (SVR range, 37%-65%) (4, 25).

In the QUEST 1/2 trials, 785 HCV GT1, treatment naïve patients were treated with Simeprevir (150 mg daily), pegylated interferon (PEG) and weight based ribavirin (RBV) for 24 or 48 weeks according to their virological response during therapy. The SVR12 was 75% for GT1a and 85% for GT1b. Adverse events included increases in bilirubin and photosensitivity. The prevalence of Q80K polymorphism of the NS3 protease varied according to HCV genotype; in 1500 chronic HCV patients, 32% of GT1a and 0.1% of GT1b exhibited the polymorphism (26, 27).

In 293 HCV GT1 patients with prior relapse, PEG/RBV plus simeprevir 150 mg daily was associated with high viral responses. Importantly, the SVR12 varied according to the amount of fibrosis, with patients with liver biopsies demonstrating low fibrosis (Metavir score of F0-2) having an 82% SVR12, while those HCV GT1 patients with liver biopsies demonstrating high fibrosis (Metavir 3 and 4) the SVR 12 were lower 73% and 74%, respectively (28).

In previous null and partial responders and relapsers, response rates to simprevir-containing therapy, were lower in null responders (41%-59%) and partial responders (65%-86%) than previous relapsers (76%-89%) (4).
Importantly in both treatment-naive and treatment-experienced patients infected with HCV genotype 1a, those with a Q80K polymorphism in the NS3 region of hepatitis C virus responded less well to simeprevir

Sofosbuvir/Simeprevir (Genotype 1)
(COSMOS TRIAL)

In order to assess whether sofosbuvir and simeprevir could be used to treat patients with chronic hepatitis C GT1 infection, 167 patients were enrolled and randomized to 2 different treatment arms: cohort 1 was comprised of 80 previous non-responders (to PEG/RBV) with METAVIR scores F0-F2 and cohort 2 was comprised of 87 nonresponders and treatment naïve patients with METAVIR scores F3-F4 (bridging fibrosis/cirrhosis). The primary endpoint was sustained virologic response 12 weeks after stopping treatments (SVR 12). Patients received sofosbuvir (400 mg daily) plus simeprevir (150 mg daily, with or without RBV for 12 or 24 weeks (29).
In cohort 1, the 12 week treatment groups, SVR 12 was 96% (26/27 pts) and 93% (13/14 pts) in patients treated with or without RBV, respectively. The 24 week treatment groups had SVR 12 of 79% (19/24 pts) and 93% (14/15 pts with or without RBV, respectively (29).
In cohort 2, the 12 week treatment groups, SVR 12 was 93% (25/27 pts) and 93% (13/14 pts) in patients treated with or without RBV respectively. The 24 week treatment groups had SVR 12 of 93% (28/30 pts) and 93% (16/16 pts) with or without RBV.
Regarding responses in cohort 2, patients with chronic HCV genotype 1a and 1b infection had a treatment response ranging from 88%-100%. In HCV GT1a patients, without the Q80K polymorphism, a 93% (13/14 pts) and 87%% (7/8 pts) SVR12 rate for 12 week regimen of SOF/SMV with and without RBV, respectively was observed. In HCV GT1a patients, with the Q80K polymorphism, 87% (7/8 pts) and 100% (3/3 pts), SVR12 rate for 12 week regimen of SOF/SMV with and without RBV, respectively was observed. Of note, 100% of patients with chronic HCV genotype 1b, without regard to treatment length or presence of ribavirin experienced SVR12 Of note, in patients with cirrhosis [Metavir 4 (47% of the patients n=40)], SVR12 was 86 and 91% with and without ribavirin (29).
Importantly no patients experienced on treatment virological failure, including viral breathrough. Six patients had viral relapse after end of treatment. Of those patients who experienced viral relapse, 5 of the 6 patients had developed resistance associated mutations to simeprevir. Side effects were reported as fatigue, headache and nausea (29).

SUMMARY OF AASLD /IDSA HCV TREATMENT GUIDELINES 2014.

The AASLD/IDSA guidelines list their summary of recommendations for patients who are initiating therapy for HCV infection or who experienced a relapse after Prior PEG/RBV Therapy, by HCV genotype. For HCV genotype 1, therapy recommendations for both IFN eligible and IFN ineligible were recommended with the use of combination of PEG/RBV and either sofosbuvir (SOF) or simeprevir (SMV) and for those patients who were IFN ineligible, SOF plus SMV simeprevir ± RBV for 12 weeks or SOF + RBV for 24 weeks. For GT 2 and 3, the guidelines recommended SOF plus RBV for 12 and 24 weeks, respectively. For chronic HCV GT 4 infection, the recommendations were either SOF + PEG/RBV for 12 weeks or SOF +RBV for 24 weeks. For GT 5 and 6, both regimens contained IFN (Table 3) (5).

Table 3 Naive/Relapsers to PEG/Ribavirin (RBV)

Genotype	Recommended	Alternative
1	IFN eligible-SOF+PEG/RBV-12 wk IFN ineligible –SOF+ SMV ± RBV-12 wk	IFN eligible –SMV-12 wk + PEG/RBV -24 wk IFN ineligible –SOF+ RBV-24 wk
2	SOF + RBV – 12 wk	
3	SOF + RBV – 24 wk	SOF + PEG/RBV -12 wk
4	IFNeligible - SOF+PEG/RBV-12 wk IFN ineligible - SOF+RBV-24 wk	SMV X 12 wks + PEG/RBV - 24-48 wk
5 or 6	IFN eligible – SOF + PEG/RBV-12 wk	IFN eligible – PEG/RBV - 48 wk

The AASLD/IDSA guidelines list their summary of recommendations for patients in whom previous PEG/RBV treatment has failed. For HCV genotype 1, therapy, recommendations for both IFN eligible and IFN ineligible were recommended with the use of combination of PEG/RBV and either SOF or SMV and for those patients who were IFN ineligible, SOF plus SMV. For GT 2 and 3, the guidelines recommended SOF plus RBV for 12 and 24 weeks, respectively, For GT 4, the recommendations were SOF +PEG/RBV for 12 weeks, SOF +RBV for 24 weeks or alternatively SMV 12wk and PEG/RBV for 24-48 weeks (5) (Table 4).

Table 4
Treatment Experienced to PEG/Ribavirin (RBV)

Genotype	Recommended	Alternative
1	SOF+ SMV± RBV-12 wk	IFN eligible – SOF-12 wk + PEG/RBV -12 wk SMV-12 wk + PeG/RBV – 24 wk
2	SOF + RBV – 12 wk	SOF + PEG/RBV -12 wk
3	SOF + RBV – 24 wk	SOF + PEG/RBV -12 wk
4	IFN eligible - SOF-12 wk + PEG/RBV -12 wk IFN ineligible SOF + RBV – 24 wk	SMV-12 w + PEG/RBV – 24-48 wk
5 or 6	IFN eligible-SOF – 12wk +PEG/RBV-12wk	IFN ineligible – SOF+RBV 24 wk

FUTURE
ClLINICAL TRIALS
Select Investigational Medications in Late Phase Clinical Development
New interferon free regimens consisting of combinations of NS5A and NS5B inhibitors as well as protease, NS5A and NS5B inhibitor combinations were tested in both open label trials and double blinded randomized trials. Patients with chronic hepatitis C who were treatment naïve or who had been previously treated, including those patients who had been treated with previous

protease inhibitors, like telaprevir and boceprevir were included in some of the trials (30, 31). In this part of the protocol, data from all oral regimens of select investigational medications in late phase clinical development will be summarized.

NS5A Replication Complex Inhibitors

Sofosbuvir/Ledipasvir – HCV Genotype 1 (Treatment Naïve)

(ION-1)

One of the initial trials to assess the effect of the NS5B polymerase inhibitor with an NS5A replication complex inhibitor was the ION trial in treatment naïve patients with chronic hepatitis C, genotype 1. The ION trial evaluated the fixed dose combination of sofosbuvir (400 mg daily)/Ledipasvir (90 mg daily) for 12 weeks or 24 weeks in 865 treatment-naive patients with chronic HCV genotype 1 (GT) 1. Of note, 16% of the patients had evidence of cirrhosis. The overall sustained virological response at 12 weeks (SVR12) for patients with genotype 1 infection was 99% and 98% for 12 week and 24 week treatment arms respectively. SVR12 did not differ substantially with the addition of ribavirin (97% and 99%, respectively) (32).

Sofosbuvir/Ledipasvir Genotype 1 (Treatment-Experienced)

(ION-2)

Subsequent trials were performed in order to assess this fixed dose combination treatment combination in treatment-experienced patients. The ION-2 trial assessed the response rate of this combination with and without ribavirin in the treatment experienced patients. Specifically, this trial evaluated the fixed dose combination of sofosbuvir (400 mg daily)/ledipasvir (90 mg daily) with or without ribavirin for 12 weeks or 24 weeks in 440 treatment-experience patients with chronic HCV genotype (GT) 1. Of note, 20 percent of the patients had evidence of cirrhosis. Importantly, 79% of the HCV GT1 patients had the more difficult to treat subtype, HCV GT1a. The overall sustained virological response at 12 weeks post treatment (SVR12) for treatment experienced patients with HCV GT1 infection was 94% and 99% for 12 week and 24 week, respectively. SVR12 did not differ substantially with the addition of ribavirin (96% and 99%, respectively). Importantly, all 427 patients who had a sustained virologic response at 12 weeks after the end of treatment also had a sustained virologic response at 24 weeks after end of treatment. No patient discontinued treatment owing to adverse events. The most common adverse events were fatigue, headache and nausea (33).

Sofosbuvir/Ledipasvir in Genotype 1 (Treatment-Naïve)

(ION 3)

In order to assess whether shorter duration of therapy would affect the efficacy of the sofosbuvir /ledipasvir fixed dose combination, the ION-3 trial was conducted. The ION-3 trial evaluated the fixed dose combination of sofosbuvir (400 mg daily)/ledipasvir (90 mg daily) for 8 weeks or 12 weeks in 647 treatment-naive patients with chronic HCV genotype (GT) 1. The overall sustained virological response at 12 weeks (SVR12) for treatment naive patients with genotype 1 infection was 94% and 95% for the 8 week and 12 week treatment arms, respectively. SVR12 did not differ substantially with the addition of ribavirin (93%) in the 8 week arm (34).

Sofosbuvir and Daclatasvir, Genotype 1, 2, and 3 (Treatment Naïve and Experienced)

(ALLY)

In order to assess whether a different NS5A inhibitor, Daclatasvir would be effective with the NS5B polymerase inhibitor, Sofosbuvir, in patients with HCV GT 1-3, the ALLY study was performed. Specifically, the ALLY study evaluated sofosbuvir (nucleotide analogue HCV NS5B polymerase inhibitor) and daclatasvir (HCV NS5a replication complex inhibitor in 44 HCV genotype 1 treatment naive patients and 44 HCV genotype 2 and 3 treatment naïve patients. The

patients received daclatasvir 60 mg daily and sofosbuvir 400 mg daily with or without ribavirin for 24 weeks. In a second follow up study, 82 HCV genotype 1 treatment naive patients were treated with daclatasvir plus sofosbuvir with or without ribavirin for 12 weeks and 41 patients with previous failure to telaprevir or boceprevir plus PEG/RBV were treated for 24 weeks. The primary end point was sustained virological response 12 weeks after end of treatment (SVR12). Overall, there were 211 patients treated.

Importantly similar results were noted in both the treatment naive patients with genotype 1 (n=126) and the treatment experienced with PEG/RBV and telaprevir or boceprevir (n=41) with a 98% SVR12 in both cohorts. In the previously treated groups, there were 3 of 21 patients and 6 of 20 with cirrhosis as defined by Metavir F4 score on liver biopsy. In the previously treated genotype 1 groups, the response rates were similar with and without ribavirin (100% and 95%). Of note, the SVR 12 was 92% and 89% in the genotype 2 (n=26) and 3 (n=18) groups, respectively. Side effects included fatigue, headache, nausea. Serious events included single events of gastroenteritis, colitis, stroke acute renal failure from dehydration that resolved with administration of fluid, fracture, anxiety, exacerbation of psoriasis and hypokalemia occurred. The most common grade 3 or 4 laboratory abnormalities were low phosphorus and elevated glucose levels (35).

ABT450-r, Dasabuvir and Ombitasvir Genotype 1 (Treatment Naïve and Experienced) (Sapphire)

Regimens were introduced that were designed to inhibit 3 points of the viral life cycle. These regimens consisted of the coformulation of the protease inhibitor (ABT450) (150mg daily) with ritonavir (100 mg daily), an NS5A inhibitor ombitasvir (25 mg daily) and a nonnucleoside NS5B polymerase inhibitor dasabuvir (250 mg twice daily) (referred to as the 3D regimen). ABT 450 is a potent inhibitor of NS3 and NS4 a protease and ritonavir (100 mg) allows for once daily dosing by boosting serum levels of the protease inhibitor. This combination was used in clinical trials with and without weight based ribavirin. In one of the first trials (Sapphire) patients with chronic hepatitis C genotype 1, treatment naïve patients (n=631) and treatment experienced (n=394) received this regimen with weight based ribavirin for 12 weeks. The primary end point was SVR12. Importantly, there were similar SVR 12 of 96% in both cohorts, the previously untreated and the treatment experienced patients (36).

Of note, in an abstract from Zeuzem at a recent international meeting, there were 394 patients evaluated with the 3D regimen and ribavirin. This group included 86 prior relapse patients, 65 prior partial response patients and 146 prior null response patients. The majority of patients had Metavir F0-F2 fibrosis on liver biopsy. The SVR12 rates were 95% (82/86) for patients with prior relapse 100% (65/65 for patients with prior partial response) and 95% (139/146) for patients who failed to respond to prior treatment (37).

ABT450-r, Dasabuvir and Ombitasvir (3D) Genotype 1 (Treatment Naïve and Experienced)

(TURQUOISEII)

In order to evaluate ABT450-r, dasabuvir and ombitasvir with ribavirin, a study entitled the TURQUOISE II study was performed. HCV genotype 1 infected adults with compensated cirrhosis, CTP A were enrolled and randomized to receive 12 weeks (n=208) or 24 weeks (n=172) of treatment with 3D combination with ribavirin (39, 40). Approximately 60% of the patients were treatment experienced with 36% null responders. SVR 12 rates for 12 week and 24 weeks regimens were 92% (191/201 pts) and 96% (165/172 pts), respectively. Patients with HCV genotype 1a with a null response from prior treatment demonstrated a response with SVR

12 rates of 80% and 93% for 12 and 24 weeks respectively**.** Common side effects included fatigue, headache and nausea. Hgb< 10 g per deciliter occurred in 7.2% and 11.0% of the patients in the 12 and 24 week cohorts, respectively. Overall, the discontinuation rate was 2.1% (38).

ABT450-r, Dasabuvir and Ombitasvir Genotype 1 (Treatment Naïve and Experienced) (PEARL)

In order to assess the efficacy of this combination without RBV in treatment naïve and treatment experienced patients with and without cirrhosis, there were a number of trials performed. In the PEARL 1 trial, the regimen assessed the efficacy of this combination in HCV genotype 1b patients in either treatment naïve (n=42) or treatment null responders (n=40). All of these patients had evidence of cirrhosis with Metavir score of F4. The end of treatment response was 95% and 90% for the naïve and null patients respectively. In the PEARL II study, HCV genotype 1b treatment experienced patients received the same regimen. In the PEARL III study genotype 1b patients (n=419) received the therapy while in the PEARL IV study, patients with HCV genotype 1a naïve to treatment (n=305) received the therapy. In PEARL III, the addition of ribavirin had minimal effect on SVR 12 with genotype 1b patients having an SVR12 of 99.5% and 97%, respectively. In PEARL IV, the addition of ribavirin improved SVR 12 in genotype 1a patients from 90% (185/205) to 97% (97/100). On the basis of logistic regression analysis of baseline demographic and clinical characteristics, only IL28CC genotype was associated with an increased rate of sustained virologic response among patients with HCV genotype 1a infection (p=.03) (39, 40).

Asunaprevir and Daclatasvir Genotype 1b (Treatment Experienced and Naïve) (HALLMARK- DUAL)

The HALLMARK-DUAL trial was a phase 3 study with asunaprvir and daclatavir (DUAL) for null or partial responders to pegylated interferon and ribavirin, patients who were intolerant to or ineligible for pegylated interferon and ribavirin and treatment naïve patients with HCV genotype1b. There were 305 treatment naïve patients and 203 patients who had achieved a prior partial or null response. The trial examined the efficacy of daclatasvir 60 mg daily plus asunaprevir 100 mg twice daily in patients with HCV genotype 1b with and without cirrhosis. There were 203 patients who had achieved a prior partial response or null response to PEG/RBV and 235 patients who were ineligible for or intolerant to PEG/RBV. The SVR 12 were 90% (182/203 for treatment naïve patients), 82% (98/119 for prior null responders) and 81% (68/84 for prior partial responders) and 82% 192/235 for patients who were intolerant to or ineligible for PEG/RBV. For the 77 patients with advance fibrosis and/or cirrhosis with thrombocytopenia, the SVR12 was 73%. (41).

SPECIAL POPULATIONS

Patients Compensated Cirrhosis

In general, clinical trials of regimens using new direct acting antiviral agents did not include patients with decompensated cirrhosis. When subset analysis was performed, those patients with compensated cirrhosis exhibited lower SVR12 than those patients without cirrhosis. In the subanalysis of the SOF +PEG/RBV trial, SVR 12 was 80% in the patients with cirrhosis (n=40) versus the SVR12 of 92% in those patients without cirrhosis (23,24). Similar findings with regard to SVR12 were noted in the genotype 3 patients. Of note, these differences were not observed among patients with HCV genotype 2 patients who were treated with sofosbuvir plus ribavirin (4, 6)

The AASLD/ IDSA practice guidelines supported therapy for treatment naïve patients with compensated cirrhosis, including those patients with hepatocellular carcinoma with the same treatment genotype specific regimens as those patients without cirrhosis. Regarding the treatment of patients with Child's Turcotte Pugh (CTP B or C), the patients should be referred to an expert. If the decision to treat has been made, the recommended regimen for patients with any HCV genotype who have CPT class B or C who may or may not be candidates for OLTx, then daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks by highly experienced HCV providers (6).

References

1. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. American Association for the Study of Liver Diseases. *Hepatology*. 2009. 49:1335-74.
2. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011. 54:1433-44.
3. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006. 144:705-714.
4. Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of Hepatitis C: A Systematic Review. *JAMA.* 2014.312: 631-40.
5. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, Marinos G, Kaldor JM . Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology*. 2001.34:809-816.
6. AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.
7. Simmonds P, Bukh J, Combet C, Deléage G, Enomoto N, Feinstone S, Halfon P, Inchauspé G, Kuiken C, Maertens G, Mizokami M, Murphy DG, Okamoto H, Pawlotsky JM, Penin F, Sablon E, Shin-I T, Stuyver LJ, Thiel HJ, Viazov S, Weiner AJ, Widell A. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes *Hepatology*. 2005. 42:962-73.
8. Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol*. 2007.5:453-63.
9. Langel CM, Jacobson IM, Rice CM, Zeuzem S. Emerging therapies for the treatment of hepatitis C. *EMBO Mol Med*. 2014. 6:4–15.
10. Pokros PJ. New Direct-acting Antivirals in the Development for Hepatitis C Virus Infection. *Ther Adv Gastroenterol*. 2010. 3:191-202.

Pharmaceutical Agents

11. Welsch C1, Jesudian A, Zeuzem S, Jacobson I. New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. *Gut.* 2012. 61 Suppl 1:i36-46.
12. .Rosenquist Å, Samuelsson B, Johansson PO, Cummings MD, Lenz O, Raboisson P, Simmen K, Vendeville S, de Kock H, Nilsson M, Horvath A, Kalmeijer R, de la Rosa G, Beumont-Mauviel M Discovery and development of simeprevir (TMC435), a HCV NS3/4A protease inhibitor. *J Med Chem.* 2014. 57:1673-93.
13. Kiser, JJ, Burton JR Everson G. Drug–drug interactions during antiviral therapy for chronic hepatitis C *Nat Rev Gastroenterol Hepatol*. 2013. 10: 596-606.

14.Scola PM, Sun LQ, Wang AX, Chen J, Sin N, Venables BL, Sit SY, Chen Y, Cocuzza A, Bilder DM, D'Andrea SV, Zheng B, Hewawasam P, Tu Y, Friborg J, Falk P, Hernandez D, Levine S, Chen C, Yu F, Sheaffer AK, Zhai G, Barry D, Knipe JO, Han YH, Schartman R, Donoso M, Mosure K, Sinz MW, Zvyaga T, Good AC, Rajamani R, Kish K, Tredup J, Klei HE, Gao Q, Mueller L, Colonno RJ, Grasela DM, Adams SP, Loy J, Levesque PC, Sun H, Shi H, Sun L, Warner W, Li D, Zhu J, Meanwell NA, McPhee F. The discovery of asunaprevir (BMS-650032), an orally efficacious NS3 protease for the treatment of hepatitis C virus infection. *J Med Chem.* 2014.13:1730-52.
15.Ludmila Gerber, Tania M. Welzel and Stefan Zeuzem New therapeutic strategies in HCV: polymerase inhibitors 2013. *Liver International.* 2013. 33, suppl 1, 85–92.
16.Murakami E, Tolstykh T, Bao H, Niu C, Steuer HM, Bao D, Chang W, Espiritu C, Bansal S, Lam AM, Otto MJ, Sofia MJ, Furman PA. Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977. *J. Biol. Chem*. 2010. 285: 34337–47.
17.Sofia MJ, Bao D, Chang W, Du J, Nagarathnam D, Rachakonda S, Reddy PG, Ross BS, Wang P, Zhang HR, Bansal S, Espiritu C, Keilman M, Lam AM, Steuer HM, Niu C, Otto MJ, Furman PA. Discovery of a β-d-2'-deoxy-2'-α-fluoro-2'-β-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. *J Med Chem. 2010*. 53:7202-18.
18.Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, Everson GT, Kwo P, Foster GR, Sulkowski MS, Xie W, Pilot-Matias T, Liossis G, Larsen L, Khatri A, Podsadecki T, Bernstein B. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med.* 2014.370:222-32.
19.Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, Heckaman M, Larsen L, Menon R, Koev G, Tripathi R, Pilot-Matias T, Bernstein B. Exploratory study of oral combination antiviral therapy for hepatitis C.*N Engl J Med*.2013.368:45-53.
20.Taylor JG, Xu L, Mitchell M, Guo H, Liu H, Kato D, Kirschberg T, Sun J, Squires N, Parrish J, Keller T, Yang ZY, Yang C, Matles M, Wang Y, Wang K, Cheng G, Tian Y, Mogalian E, Mondou E, Cornpropst M, Perry J, Desai MC. Discovery of ledipasvir (GS-5885): a potent, once-daily oral NS5A inhibitor for the treatment of hepatitis C virus infection. *J Med Chem*. 2014. 57:2033-46.
21.Belema M, Nguyen VN, Bachand C, Deon DH, Goodrich JT, James CA, Lavoie R, Lopez OD, Martel A, Romine JL, Ruediger EH, Snyder LB, St Laurent DR, Yang F, Zhu J, Wong HS, Langley DR, Adams SP, Cantor GH, Chimalakonda A, Fura A, Johnson BM, Knipe JO, Parker DD, Santone KS, Fridell RA, Lemm JA, O'Boyle DR 2nd, Colonno RJ, Gao M, Meanwell NA, Hamann LG. Hepatitis C Virus NS5A Replication Complex Inhibitors: The Discovery of Daclatasvir *J Med Chem.* 2014. 57:2013-32.
22.DeGoey DA, Randolph JT, Liu D, Pratt J, Hutchins C, Donner P, Krueger AC, Matulenko M, Patel S, Motter CE, Nelson L, Keddy R, Tufano M, Caspi DD, Krishnan P, Mistry N, Koev G, Reisch TJ, Mondal R, Pilot-Matias T, Gao Y, Beno DW, Maring CJ, Molla A, Dumas E, Campbell A, Williams L, Collins C, Wagner R, Kati WM. Ombitasvir - Discovery of ABT-267, a pan-genotypic inhibitor of HCV NS5A. *J Med Chem*. 2014. 57:2047-57.

Clinical Trials- Sofosbuvir

23. **FISSION and NEUTRIN**O Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J,

Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection. *N Engl J Med*. 2013. 368:1878-1887.
24.**FUSION/POSITRON**. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR; POSITRON Study; FUSION Study. Sofosbuvir for Hepatitis C Genotype 2 or 3 in Patients without Treatment Options. *N Engl J Med.* 2013. 368:1867-1877.

Simeprevir

25.Fried MW, ButiM, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology*. 2013. 58:1918-1929.
26.**QUEST 1** Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, Craxi A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Scott J, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial *Lancet.* 2014. S0140-6736: 60494-3.
27.**QUEST 2** Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott J, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2014. S0140-6736: 60538.
28.**PROMISE** Forns X, Lawitz E, Zeuzem S. Gane EJ, Bronowicki JP, Andreone P, Horban A, Brown AS, Peeters M, Lenz O, Kouwerkerk-Mahadevan S, Scott JA, Kalmeijer R, De La Rosa G, Sinha R, Beaumont-Mauviel M. Simeprevir (TMC 435) with peg interferon a 2a/ribavirin for treatment of chronic HCV genotype 1 infeciton in patients who relapsed after previous interferon based therapy: efficacy and safety in patient subpopulations in the PROMISE phase II trial. *Hepatology* 2013:58 Suppl 7373 A.
29.**COSMOS** Lawitz E, Sulkowski MS, Ghalib R, RodriguezTorres M, Younossi ZM Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fevery B, Lambrecht T, Ouwerkerk-Mahadevan S, Callewaert K, Symods WT, Picchio G, Lindsay KL Beaumont M and Jacobson I Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *The Lancet*, online pub 28 July 2014doi:10.1016/S0140-6736(14)61036-9

Sofosbuvir/Ledipasvir

30.Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE 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.* 2014.383:515-523.
31. Hellarda ME and Doyle JS. Interferon-free hepatitis C treatment: one pill to fit all? *Lancet*. 2014. 383: 491–492
32.**ION 1** Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian

GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. 2014. 370: 1889-1898.

33.**ION 2** Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med*. 2014. 370:1483-93.

34.**ION 3** Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herring R, Di Bisceglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW; ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014. 370:1879-88.

Sofosbuvir/Daclatasvir

35.**ALLY** Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM; AI444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection *N Engl J Med.* 2014. 370:211-21.

ABT-450R, Ombitasvir and Dasabuvir

36. **SAPPHIRE1** Feld JJ, Kowdley K, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, and Bernstein B, Treatment of HCV with ABT-450/r– Ombitasvir and Dasabuvir with Ribavirin *N Engl J Med.* 2014 370: 1594-1603

37.**SAPPHIRE II** Zeuzem S, Jacobson I, Baykal T et al phase 3 placebo controlled study of interferon free 12 week regimen of ABT 450 /R ABT 267, ABT 333 and ribavirin intreatment experienced adults with hepatitis C virus genotype 2. *J Heptol*. 2014: 50 S, S1.

38.**TURQUOISE II** Poordad F, Hezode C, Trinh R, et al. SVR 12 rates of 92 and 96% in 380 hepatitis C virus genotype 1 infected adults with compensated cirrhosis treated with ABT 450/R ABT 267 and ABT 333 plus ribavirin (3D + Ribavirin J *Hepatol.* 2014. 50 Sup. S523.

39.Poordad E, Hezode C, Trinh R et al ABT 450/R Ombitasavir and Dasabuvir with ribavirin for hepatitis C with cirrhosis, *N Engl J Med .2014.* 370:1973-1982.

40.**PEARL III/IV** Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Janczewska E, Rizzardini G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR.ABT 450R-Ombitasvir and Dasbuvir with or without Ribavirin for HCV. *N Engl J Med* 2014. 370:198-1992.

Daclatasvir/Asunaprevir Trials

41.**DUAL HALLMARK** Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY Chang T-T, MD, Everson GT, Heo J, Gerken G, Yoffe B, Towner WJ Bourliere B, Metivier S, Chu CJ, Sievert W, Bronowicki JP MD, Thabut D, Lee YJ. Kao JH, McPhee F, Kopit J, Mendez P, Linaberry M, Hughes E, Noviello S. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. *The Lancet*. 28 July 2014 DOI: 10.1016/S0140-6736(14)61059.

Appendix 1
Drug-drug Interactions during antiviral therapy for chronic hepatitis C

Protease inhibitors				
Drugs	**Route of metabolism or excretion**	**CYP effects**	**Transporter substrate**	**Transporter effects**
ABT450/ritonavir	CYP3A	CYP3A inhibition by ritonavir	ND	Inhibits OATP1B1
Asunaprevir	ND	Moderate inhibitor of CYP2D6; weak inducer of CYP3A4	OATP1B1/2B1	Weak P-gp and OATP1B1/1B3 inhibitor
Boceprevir	CYP3A, AKR	Moderate CYP3A inhibitor	P-gp	Weak P-gp inhibitor
Simeprevir	CYP3A	Mild inhibitor of CYP1A2 and intestinal CYP3A37	ND	OATP1B1 and MRP2 inhibitor
Telaprevir	CYP3A	Strong CYP3A inhibitor	P-gp	Moderate P-gp inhibitor
NS5A inhibitors				
ABT267	ND	ND	ND	ND
Daclatasvir	CYP3A	ND	P-gp44	Moderate P-gp and OATP1B1 inhibitor
Ledipasvir	ND	Not a CYP inhibitor or inducer	P-gp	Weak inhibitor of P-gp, BCRP, OATP1B1, OATP1B3
Nucleos(t)ide polymerase inhibitors				
Sofosbuvir	Renal	ND	P-gp	ND
Non-nucleoside polymerase inhibitors				
ABT333	CYP2C8, CYP3A4 and CYP2D6			
	contribute approximately 60%, 30%, and 10% to ABT-333 metabolism, respectively	ND	ND	ND
Abbreviations: AKR, aldoketoreductase; BCRP, breast cancer resistance protein; CYP, cytochrome P450; DAA, direct-acting antiviral agent; MRP, multidrug resistance protein; NA, not applicable; ND, no data; OATP1, organic anion transporting polypeptide; P-gp, P-glycoprotein; UGT, uridine glucuronyl transferase.				

Adapted from Kiser JJ et al. Nature Reviews Gastroenterology & Hepatology 2013.10:596-606.