TITLE: **Holkira (Ombitasvir/Paritaprevir/ Ritonavir with Dasabuvir) and Harvoni (Ledipasvir/Sofosbuvir) for Chronic Hepatitis C: A Review of the Clinical Evidence**

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CONTEXT AND POLICY ISSUES

An estimated 250,000 Canadians (approximately 1% of the population) have chronic hepatitis C (CHC) infection, which peaks in prevalence in young to middle-aged adults (the 30 to 59 year age group).[1,2] There are six main genotypes of hepatitis C virus (HCV), the most prevalent in Canada is genotype 1 (approximately 65% of HCV infected patient population). Within genotype 1 there are two main subtypes (1a and 1b), with 1a being more prevalent.[2]

Following acute infection with HCV, typically an asymptomatic infection, the risk of developing CHC is high, with approximately 50% to 85% of individuals remaining positive for HCV ribonucleic acid (RNA).[3] As with acute infection, CHC is often asymptomatic or can be 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.[3] Over the long term, complications may arise, with approximately 15% to 20% of individuals with CHC developing end-stage liver disease over 20 years of infection.[4]

Candidates for antiviral therapy in CHC include patients with compensated liver disease, who do not have contraindications to treatment, and who are willing to undergo treatment.[5] The goal of antiviral therapy is to achieve a sustained virologic response (SVR – defined as aviremia) at least 24 weeks after the end of treatment.[5] The choice of treatment takes into consideration a variety of factors, including expected efficacy, duration of the regimen, and adverse effect profile.[6] Until recently, treatment regimens for CHC have included interferon, which has several disadvantages including potential for treatment limiting adverse effects, inconvenience of administration via injection, and potentially extended treatment duration (up to 48 weeks). Oral interferon-free regimens for the management of genotype 1 CHC have recently been approved for use in Canada. These regimens 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 DAAs target proteins involved with the replication of the HCV and

include NS5B nucleotide polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A replication complex inhibitors.[7]

Holkira Pak (ombitasvir/paritaprevir/ritonavir + dasabuvir) was recently approved for use by Health Canada for the treatment of adults with genotype 1 CHC (including patients with compensated cirrhosis).[10] Specifically, it is approved in combination with ribavirin (RBV) in non-cirrhotic patients with genotype 1a infection, without RBV in non-cirrhotic patients with genotype 1b infection, and with RBV in patients with compensated cirrhosis.[10] Holkira Pak combines three DAAs with differing mechanisms of action (12.4 mg ombitasvir, 75 mg paritaprevir, and 50 mg ritonavir) with 250 mg dasabuvir.[10] The combination tablets (ombitasvir/paritaprevir/ritonavir) are co-packaged with the dasabuvir tablets and dispensed in weekly cartons of each daily dose for convenience.[10]

In October of 2014, Harvoni (ledipasvir 90 mg plus sofosbuvir 400 mg as a fixed dose combination) was the first interferon-free DAA regimen to be issued a notice of compliance (NOC) in Canada.[8] This treatment is indicated for the treatment of genotype 1 CHC. Evidence suggests that Harvoni is well-tolerated, with reduced treatment duration and high SVR rates.[9]

The treatment of CHC using the all oral, interferon-free regimen has potential advantages compared with interferon-based regimens. This report reviews the evidence of clinical effectiveness and safety of Harvoni and Holkira Pak for the management of CHC genotype 1, which may assist in healthcare funding decision-making in the context of the publicly funded healthcare system. Due to the complex generic names, the trade names of these therapies will be used in the review for clarity.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of Holkira Pak (ombitasvir/paritaprevir/ ritonavir plus dasabuvir) for the treatment of chronic hepatitis C genotype 1?

2. What is the clinical effectiveness and safety of Harvoni (ledipsavir and sofosbuvir) for patients with chronic hepatitis C genotype 1?

KEY FINDINGS

Six clinical trials demonstrated the superiority of Holkira Pak alone and with RBV over historical control rates for SVR12 (sustained virologic response 12 weeks after treatment). In patients with CHC genotype 1b, Holkira Pak alone was not within the pre-specified margin for non-inferiority to Holkira Pak with RBV. However, in patients with CHC genotype 1a, Holkira Pak alone was not non-inferior to the combination, indicating the need for RBV co-treatment in patients with genotype 1a.

The available evidence from six open-label clinical trials on Harvoni indicates that SVR was achieved by more than 90% of patients who received Harvoni with or without ribavirin (RBV) for 8, 12 or 24 weeks. Serious adverse events and discontinuation due to adverse events were low, and anemia, rash and depression were low in patients who did not receive RBV.

METHODS

A limited literature search for Holkira was conducted on key resources including Ovid MEDLINE, Ovid Embase, PubMed, Canadian and major international health technology assessment agencies, as well as a focused Internet search. The search was not limited by publication date, and was conducted December 17, 2014 with alerts conducted until January 12, 2015. Results were not limited by language or methodology.

For the search for Harvoni, a limited literature search was conducted on key resources including PubMed, Ovid Medline, Ovid EMBASE, The Cochrane Library (2014, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology assessment agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2011 and May 28, 2014. Alerts were conducted until January 12, 2015.

Studies on cost-effectiveness of both Holkira and Harvoni were searched, but no studies were identified.

Selection Criteria and Methods

One reviewer screened citations and selected studies. A second reviewer screened the search alerts of citations and selected studies retrieved on Harvoni from May to Dec 2014. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with chronic hepatitis C genotype 1
Intervention	Ombitasvir/paritaprevir/ritonavir with dasabuvir (Holkira) OR ledipasvir 90 mg + sofosbuvir 400 mg (Harvoni)
Comparator	Other treatments for hepatitis C
Outcomes	Clinical effectiveness (e.g. sustained virologic response)
Study Designs†	Health technology assessment reports, systematic reviews, meta-analyses, pivotal* randomized controlled trials

*Pivotal RCTs were those studies considered by Health Canada for the approval of Holkira Pak, as identified in the product monograph

† Relevant conference abstracts on Holkira were not summarized or critically appraised, but were placed in an appendix for information purposes due to the possibility of emerging evidence on this newly approved drug.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications or conference abstracts, or were published outside of the timeframe of the search. Review articles that were not based upon a systematic literature search and duplicate publications of the same study were excluded from the report.

Critical Appraisal of Individual Studies

For the Holkira RCTs, the SIGN50 Checklist was used to critically appraise the studies. The included studies on Harvoni were critically appraised using the Downs and Black checklist.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE – HOLKIRA (OMBITASVIR/PARITAPREVIR/RITONAVIR WITH DASABUVIR)

Quantity of Research Available

The literature search yielded 74 citations. After screening citations from the database and grey literature searches, 39 potentially relevant studies were obtained for full-text review. Of those 39 citations, five reports[18-22] containing the results of six unique pivotal RCTs were selected for inclusion. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

The characteristics of the included RCTs[18-22] can be found in Appendix 2, Table 2A. The efficacy of Holkira Pak was assessed in six randomized trials, [18-22] which differed in their included populations, design and comparators. The PEARL-II study[18] (n=179) and the PEARL-III study[21] (n=419) included non-cirrhotic, treatment naive patients with HCV genotype 1b only and compared the efficacy of Holkira Pak alone to Holkira Pak combined with RBV for 12 weeks duration; however, PEARL-II was an open-label study whereas in PEARL-III, treatment with RBV was double-blinded. Both studies were conducted in Europe and the United States. The PEARL-IV[21] study (n=305) also enrolled non-cirrhotic, treatment naive patients and had the same treatment arms as Pearl-II and Pearl-III with double-blinded administration of RBV, but included only those patients with HCV genotype 1a. The geographic location of PEARL-IV included Canada, the United States and the United Kingdom. The SAPPHIRE-I and SAPPHIRE-II studies compared Holkira Pak combined with ribavirin (RBV) for 12 weeks duration to placebo in non-cirrhotic, treatment naïve (SAPPHIRE-I; n=631) and treatment experienced (SAPPHIRE-II; n= 394) patients with HCV genotype 1a or 1b. Both studies were conducted in North America, Europe and Australia. The TURQUOISE-II study was an open-label randomized study that compared Holkira Pak alone for 12 weeks to Holkira Pak alone for 24 weeks in patients with HCV genotype 1a or 1b and Child-Pugh Class A cirrhosis.[22] TURQUOISE-II was conducted in Canada, the United States, the United Kingdom and Europe. All of the six studies excluded patients with HIV or Hepatitis B co-infection, a recent history of drug or alcohol abuse, and a history of uncontrolled seizures, uncontrolled diabetes and malignancy in the past five years.[18-22] In addition to these criteria, TURQUOISE-II[22] and SAPPHIRE-II[20] had exclusion criteria based upon prior use of specific medications for CHC infection.

The study outcomes were similar, with SVR12 (sustained virologic response 12 weeks after treatment), virologic failure and post-treatment relapse (virologic relapse) as the main efficacy outcomes. These outcomes were defined as follows:

- SVR12 - an HCV RNA level of <25 IU per milliliter 12 weeks after the end of study treatment.

- Virological failure - confirmed HCV RNA level of 25 IU per milliliter or more after an HCV RNA level of less than 25 IU per milliliter during treatment, a confirmed increase in the HCV RNA level of more than 1 log10 IU per milliliter above the nadir during treatment, or an HCV RNA level of 25 IU per milliliter or more at all assessments during treatment among patients who received at least 6 weeks of treatment, OR: confirmed increase from nadir in HCV-RNA level (defined as 2 consecutive HCV-RNA measurements greater than 1 log10 IU/mL greater than nadir) at any point during treatment; failure to achieve HCV-RNA level less than 25 IU/mL by week 6; and confirmed HCV-RNA level of 25 IU/mL or greater in 2 consecutive measurements at any point during treatment after HCV-RNA level was less than 25 IU/mL.
- Post-treatment relapse (virologic relapse) - confirmed HCV RNA level of 25 IU per milliliter or more between the final visit during the double blind treatment period and 12 weeks after the last dose of study drug among patients who completed treatment (duration of study-drug exposure, ≥77 days), had an HCV RNA level of less than 25 IU per milliliter at the final visit during the double blind treatment period, and had data on HCV RNA levels available after the completion of treatment.

In all studies, the SVR12 was compared to historical control rates (ranging from 47% to 78%), using a non-inferiority approach (Appendix 2, Table 2A). The non-inferiority margin was set at 10.5% in all studies, with superiority being subsequently tested if the Holkira Pak arm was found to be non-inferior to the historical control.

Summary of Critical Appraisal

Details of the critical appraisal of the included RCTs are summarized in Appendix 3, Table 3A. All studies met the majority of SIGN50 checklist internal validity criteria with appropriate and focused research questions, appropriate randomization and allocation concealment, mainly balanced baseline characteristics between treatment arms, clear definitions of outcomes, low dropout rates and analysis according to the intention to treat principle. Two studies, PEARL-II[18] and TURQUOISE-II[22], however, had open-label designs. While the primary outcome and other measures related to viral load were objective and unlikely to be affected by blinding, the reporting of adverse effects could potentially be biased by knowledge of treatment.

All studies compared the efficacy of the treatment arms to historical control rates for the primary outcome of SVR12. The validity of such a comparison is uncertain as it was unclear if the characteristics of the Holkira Pak treatment arms were similar to those of the historical control, creating the potential for bias or confounding. As well, it was unclear whether the study populations and historical controls were treated similarly with respect to the background medical care that was received. The statistical comparison to the historical control used a non-inferiority approach, with a 10.5% non-inferiority margin. There was no explanation provided to justify the selection of this value.

Summary of Findings

Main findings of included studies for all outcomes are summarized in detail in Appendix 4, Table 4A.

In all studies, the SVR12 with Holkira Pak alone or with RBV was found to be statistically superior to the historical control, with the SVR12 ranging from 90.2% to 100% with 12 weeks of treatment (Appendix 4, Table 4A).[18-22] For the comparisons between Holkira Pak alone and

Holkira Pak with RBV in patients with CHC genotype 1b,[18,21] Holkira Pak alone was found to be non-inferior to the combination with RBV. However, in patients with CHC genotype 1a, Holkira Pak alone was not within the pre-specified margin for non-inferiority to the combination including RBV.[21]

The SVR12 rates are summarized according to genotype in Table 2 below. For patients with CHC genotype 1a, the combination of Holkira Pak with RBV for 12 weeks had SVR12 rates ranging from 95.3% to 97.0% in non-cirrhotic treatment naive patients[19,21] and was 96.0%[20] in non-cirrhotic treatment experienced patients. A lower SVR12 rate for the 12 week course of treatment with Holkira Pak with RBV was observed for patients with cirrhosis (88.6%)[22] and for the 12 week course of treatment with Holkira Pak alone (90.2%).[21]

For patients with CHC genotype 1b, the combination of Holkira Pak with RBV for 12 weeks had SVR12 rates ranging from 98.0% to 99.5% in non-cirrhotic treatment naive patients[19,21] and 96.6% to 96.7% in non-cirrhotic treatment experienced patients.[18,20] Holkira Pak alone for 12 weeks achieved SVR12 of 100% and 99% in non-cirrhotic, treatment experienced[21] and treatment naive[18] patients with CHC genotype 1b, respectively. In patients with cirrhosis, the SVR12 for Holkira Pak with RBV was similar for the 12 and 24 week duration of treatment.[22]

Table 2: Summary of SVR12 rates by genotype

Study	Population	SVR-12 Holkira Pak Alone	SVR12 Holkira Pak with RBV
Genotype 1a			
Ferenci 2014[21] – PEARL-IV	Non-cirrhotic treatment naive	90.2%	97.0%
Feld 2014[19] – SAPPHIRE-I	Non-cirrhotic treatment naive	-	95.3%
Poordad 2014[22] – TURQUOISE-II	Treatment naive or treatment experienced with cirrhosis	-	88.6%[A] 94.2%[B]
Zeuzem 2014[20] – SAPPHIRE-II	Non-cirrhotic, treatment experienced	-	96.0%
Genotype 1b			
Andreone[18] – PEARL-II	Non-cirrhotic, treatment experienced	100%	96.6%
Ferenci 2014[21] – PEARL-III	Non-cirrhotic treatment naive	99%	99.5%
Feld 2014[19] – SAPPHIRE-I	Non-cirrhotic treatment naive	-	98.0%
Poordad 2014[22] – TURQUOISE-II	Treatment naive or treatment experienced with cirrhosis	-	98.5%[A] 100%[B]
Zeuzem 2014[20] – SAPPHIRE-II	Non-cirrhotic, treatment experienced	-	96.7%

A – 12 week regimen; B – 24 week regimen; RBV - Ribavirin

Other Efficacy Outcomes

Very few patients experienced virologic failure or post-treatment relapse (Appendix 4, Table 4A), regardless of genotype, prior treatment experience, or cirrhosis. Normalization of ALT was assessed in SAPPHIRE-I and SAPPHIRE-II, in comparison with placebo. In SAPPHIRE-I, 97% of patients treated with Holkira Pak with RBV had a normalization of ALT versus 14.9% with placebo ($p<0.001$).[19] In SAPPHIRE-II the normalization of ALT with Holkira Pak with RBV was 96.9% versus 12.8% with placebo ($p<0.001$).[20]

Adverse Effects

Adverse effects are summarized in Appendix 4, Table 4A.The most commonly reported adverse effects were fatigue, nausea, and headache. Discontinuation of treatment due to an adverse event was low, ranging from 0% to 2.3%.

SUMMARY OF EVIDENCE – HARVONI (LEDIPSAVIR/SOFOSBUVIR)

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Quantity of Research Available

A total of 556 citations were identified in the literature search. Following screening of titles and abstracts, 531 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 24 publications were excluded for various reasons, while 6 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection. Additional references of potential interest, including conference abstracts, are provided in Appendix 5.

Summary of Study Characteristics

Characteristics of the included studies are summarized below. Details are provided in Table 2B of Appendix 2.

Six clinical trials published in 2014, assessing treatment with Harvoni were identified.[12-17] Four studies[13-15,17] included patients from the US, one study[16] enrolled patients from New Zealand, and one study[12] enrolled patients from the US, France, Germany, Italy, Spain, Puerto Rico, and the UK. Two studies[12,13] included patients who were treatment naïve, two studies[14,17] included only treatment experienced patients, and two included treatment naïve patients and patients who had previously received treatment.[15,16] The number of patients included in these studies ranged from 14 to 865. Even though most of these trials allocated treatment by randomization, there was no control group who received no treatment or an interferon-based regimen. In addition one trial[17] included only one treatment arm and no comparison groups. Treatments assessed in these clinical trials were the combination Harvoni[12-17] and Harvoni plus RBV for 6 weeks to 24 weeks.[12-16] One study[16] also investigated the combination of sofosbuvir plus GS9669 (a nonnucleoside inhibitor of HCV) and RBV. The follow-up period was 12 and 24 weeks after the end of therapy. Sustained virological response at 12 weeks[12-17] or at 24 weeks[14,15] after the end of therapy was reported in all the trials.

Summary of Critical Appraisal

Detailed critical appraisal points are presented in Table 3B of Appendix 3.

Similar appraisal points that were reported for the Holkira trials are also relevant for the Harvoni trials. All six clinical trials[12-17] stated the objective and the selection criteria and described patient characteristics, interventions, and outcomes. These trials however lacked a concurrent prospective control group. Open-label design was used in all trials, so patients and investigators

were not masked to treatment allocation. However, three clinical trials[12-14] indicated that post treatment HCV RNA results were blinded to the investigator and sponsor. A sample size calculation was reported in three clinical trials.[12-14] No power calculation was reported for the other studies.[15-17] Four trials[12,13,15,17] reported results using either intention-to-treat analyses or including all the patients who underwent randomization and received treatment in the analyses. The proportion of patients who discontinued treatment due to adverse events ranged between 0% and 5%. Generalizability of findings to broader HCV patient populations (such as pediatrics) is unclear.

Summary of Findings

Detailed study findings are presented in Table 4B of Appendix 4.

In treatment naïve patients who received 24 weeks of treatment with Harvoni or Harvoni + RBV, SVR12 was achieved by 98% and 99% respectively.[12] In those treated with Harvoni for 12 weeks, 95% to 99% achieved SVR12,[12,13,15] and 97% to 100% who received Harvoni plus RBV achieved SVR12.[12,16] In patients who received Harvoni with or without RBV for eight weeks, SVR12 occurred in 93% to 100% of patients.[13,15] Treatment with Harvoni plus RBV for six weeks resulted in 68% of patients achieving SVR12.[16]

In treatment experienced patients who received Harvoni for 12 weeks, SVR12 was achieved by 94% to 100%.[14,15,17] In patients who received Harvoni plus RBV for 12 weeks, 96% to 100% achieved SVR12.[14-16] Most (95% to 100%) patients who received Harvoni with or without RBV for 24 weeks achieved SVR12.[14,16] In summary, SVR12 was achieved by the majority of patients who received Harvoni of various durations, with and without RBV, and regardless of previous treatment.

The proportion of patients who experienced a serious adverse event (SAE) ranged between 0% and 8%, with the highest proportion of SAEs reported in patients who received Harvoni for 24 weeks.[12] One trial did not report SAEs.[16] The proportion of patients who discontinued treatment due to adverse events ranged from 0% to 4%, with the highest rate reported in patients who received Harvoni plus RBV for 12 weeks.[16] Anemia rates ranged from 0% to 1% in patients who received a RBV free regimen. In those who received RBV, anemia rates ranged from 8 to 12% and were highest in those who received Harvoni plus RBV for 12 weeks.[14] Three studies[15-17] did not report rates of anemia. Rash rate ranged from 0% to 16%, with the highest rates in patients who received Harvoni plus RBV for 12 weeks.[16] Depression was only reported by one trial,[16] and rates ranged from 0 to 22%, with the highest rates in patients who received Harvoni plus RBV for 12 weeks.[16]

LIMITATIONS

The results of the presented evidence should be interpreted in light of the following limitations. The six RCTs that assessed the efficacy and safety of Holkira Pak alone or in combination with RBV had a number of common design features, such as the inclusion and exclusion criteria for study participants, the selection of the non-inferiority margins and the comparison to historical controls for the primary efficacy analysis.

Notable exclusions were patients with cirrhosis,[18-21] HIV, or Hepatitis B co-infection,[18-22] and uncontrolled seizures, uncontrolled diabetes, and malignancy.[18-22] The generalizability of the results of the included studies to these populations is, therefore, unknown. All studies included

patients aged 18 to 70 years and, as such, the results may not be generalizable to other age groups. Also relevant is the exclusion of patients with recent history of drug or alcohol abuse, the rationale being that adherence to the protocol may be problematic in this group. However, in a 'real world' setting this group is likely to be relevant and the efficacy of treatment with Holkira Pak in this group remains unknown.

For the Harvoni trials, all were open label. Most of the included clinical trials were of small sample size and power was not calculated or described by some trials. When reported, historical control rate was used to calculate power and sample size for the trials. None of the trials included control arms, as all trials investigated different treatment combinations of Harvoni with or without RBV for different durations, and none of the trials did a comparison between different treatment arms. The results of these studies are restricted to the patient populations of focus, limiting generalizability to other sub-groups. Moreover, none of the clinical trials were conducted in Canada, so applicability in the Canadian setting is unclear. Adverse effects, especially depression, were insufficiently and inconsistently reported. In addition, adverse events in the trials with small sample sizes may overestimate or underestimate rates of adverse events.

For the primary outcome of SVR12, the efficacy of Holkira Pak was compared to historical control rates using non-inferiority designs. The rationale for selection of the non-inferiority margin of 10.5% was not stated; however, it should also be noted that subsequent testing of superiority (after non-inferiority was found) found Holkira Pak was superior to the historical control rate. Thus, while there was no rationale for the non-inferiority margin, the finding of superiority makes this less problematic in terms of interpretation.

The use of the historical control has some important limitations. While the included studies were randomized, the statistical comparison for the primary efficacy outcome of SVR12 was made to a historical control. This approach is not equivalent to randomizing participants to treatment or control and then making a statistical comparison between groups. The use of a historical control does not confer the benefit of equally distributing known and unknown confounding factors. Thus, it is uncertain as to whether differences in the SVR12 between the treatment arms and historical controls were solely due to the intervention and not related to an unknown confounding factor. Further, given that the characteristics of the historical controls were not reported, it is unclear how similar the two groups of patients were, thereby decreasing the confidence in the findings. Moreover, it is unclear that the historical control (patients who were previously treated with peginterferon–ribavirin or with telaprevir and peginterferon– ribavirin) aligns with current practice. Thus, the relevance of a comparison to these treatment regimens is unclear.

There were no studies identified that compared Holkira Pak directly to other standard regimens for CHC genotype 1 infections. Thus, the comparative efficacy of Holkira Pak to other oral and interferon-based regimens remains uncertain.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Overall, clinical evidence from open label trials suggests high SVR rates and low adverse event occurrence for Holkira and Harvoni. The trials on Holkira reported SVR12 rates exceeding 90% for most treatment arms, the exception being Holkira Pak alone for 12 weeks in genotype 1a patients with cirrhosis. The primary efficacy outcome of SVR12 in comparison with historical control rates demonstrated superiority of the Holkira Pak over the control in all studies; however,

the use of the historical control rate has some limitations, as noted. In patients with genotype 1b, Holkira Pak alone was non-inferior to the combination with RBV for 12 weeks, but not for genotype 1a. Consistent with this, the approved use and labelling for Holkira Pak for patients with CHC genotype 1a is in combination with RBV, but alone for patients with CHC genotype 1b. While 12 weeks duration of treatment appeared to be adequate to achieve acceptable SVR12 rates for most groups of patients, the 12 week regimen of Holkira Pak with RBV in patients with cirrhosis and genotype 1a was less effective than the 24 week regimen. The efficacy of Holkira Pak in some important subgroups (patients with HIV or Hepatitis B co-infection, patients with a recently history of drug or alcohol abuse) remains uncertain, as does its efficacy in comparison to other oral treatments for CHC genotype 1 infection. There were no studies of the cost-effectiveness of Holkira Pak in patients with CHC genotype 1; thus, its cost-effectiveness remains uncertain.

More than 90% of patients who received Harvoni with or without RBV for 8, 12, or 24 weeks also achieved SVR 12 or 24, similar to Holkira. Even in treatment-experienced cirrhotic patients who are usually difficult to treat, 70% to 100% of patients who received Harvoni with or without RBV for 12 weeks achieved SVR12.[16] Serious AEs and discontinuation due to AE were low. Anemia, rash and depression (commonly seen in patients who receive interferon regimens) were low in patients who did not receive RBV.

Patients with HCV are at risk of increased morbidity and mortality. Current treatments with interferon can result in a range of undesirable side effects whereas interferon-free protocols have shown high SVR rates and low adverse event rates in clinical trials. There are no head to head clinical trials comparing interferon-free regimens with regimens including interferon, limiting assessment of comparative effectiveness.

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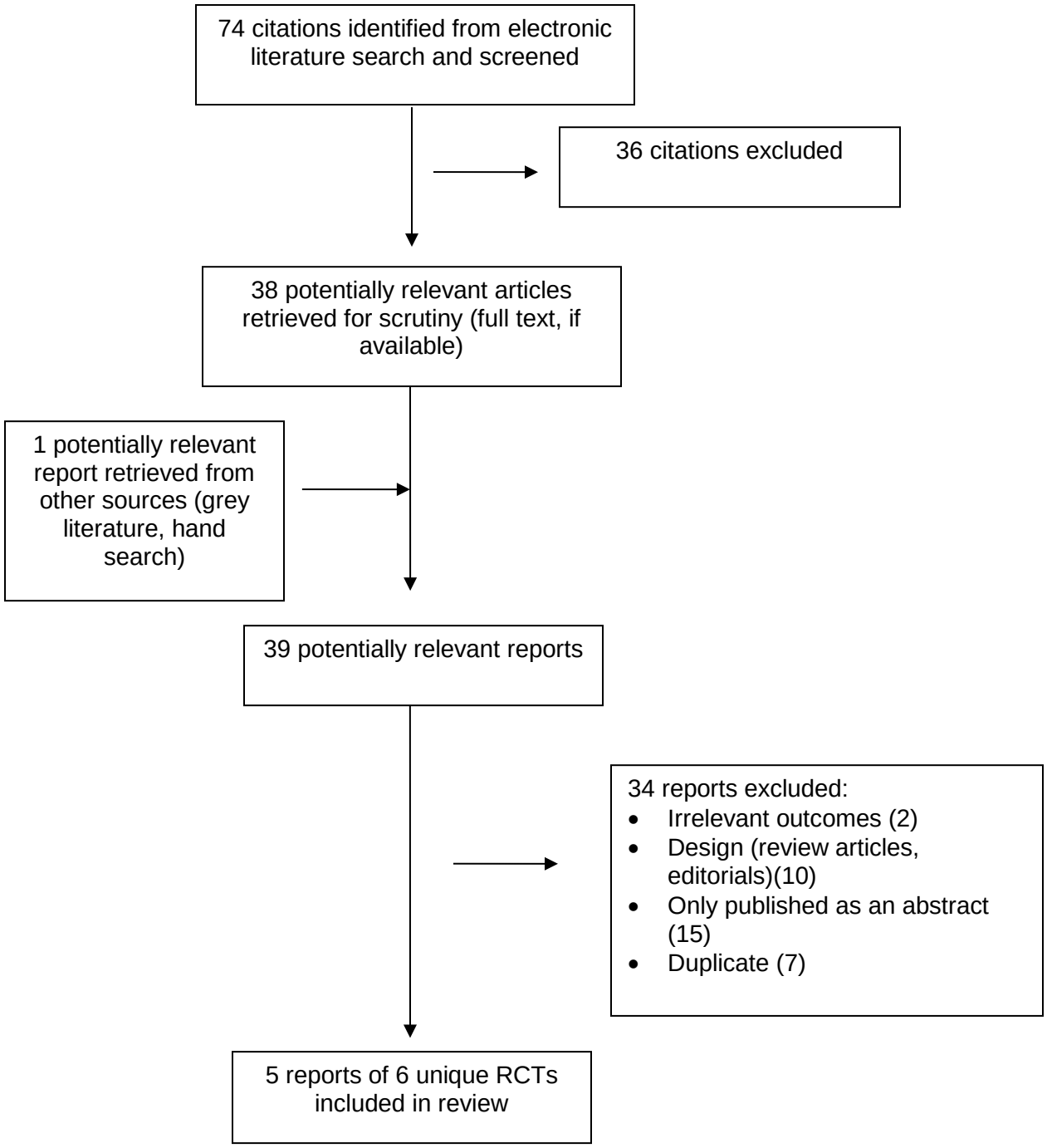
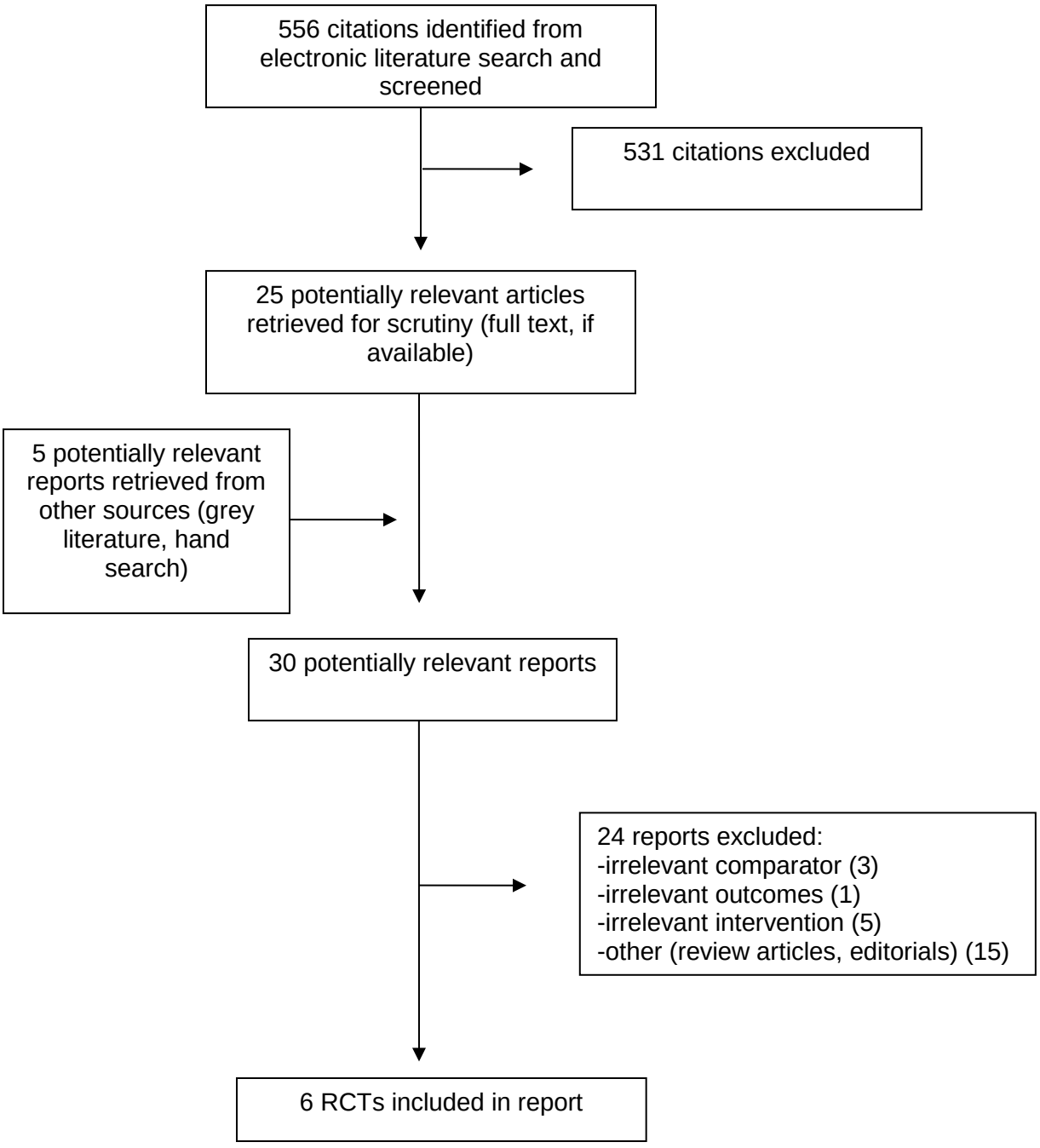
APPENDIX 1A. Selection of Included Studies - Holkira



APPENDIX 1B: Selection of Included Studies - Harvoni



APPENDIX 2: Characteristics of Included Publications

Table 2A: Characteristics of Included Clinical Studies – Holkira

First Author, Publication Year, Country Design	N	Population	Country	Key Exclusions	Treatment Arms	Outcomes
Andreone 2014[18] – PEARL-II Phase III open- label RCT	179	Non-cirrhotic, treatment-experienced patients between the ages of 18 and 70 with HCV genotype 1b	Europe and the United States	Hepatitis B surface antigen or anti–human immunodeficiency virus (HIV) antibodies Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. History of uncontrolled seizures, uncontrolled diabetes, active or suspected malignancy or history of in the past 5 years. Current or past clinical evidence of cirrhosis Specified concomitant medications, including those contraindicated for use with ribavirin and ritonavir	HOLKIRA PAK[A] FOR 12 WEEKS HOLKIRA PAK[A] + RBV[B] FOR 12 WEEKS	SVR12* Virologic failurepost treatment relapse Adverse effects *For SVR12, the non-inferiority of both regimens compared with a historical control rate was tested (75%), as was the non-inferiority between treatment arms (NI margin of 10.5%). The historical control was treated with telaprevir plus peginterferon–ribavirin.
Feld 2014[19] – SAPPHIRE-I **Phase III double-blind, placebo-controlled RCT**	631	noncirrhotic, treatment-naive patients between the ages of 18 and 70 with hcv genotype 1a (68%) or 1b (32%)	North America, Australia, Europe	Hepatitis B surface antigen or anti–human immunodeficiency virus (HIV) antibodies Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. History of uncontrolled seizures, uncontrolled diabetes, active or suspected malignancy or history of in the past	HOLKIRA PAKA + RBVB FOR 12 WEEKS PLACEBO FOR 12 WEEKS	Svr12* Virologic failure Post treatment relapse Normalization of alt Adverse effects *for SVR12, the non-inferiority to a historical control rate (78%) was tested, with a ni margin of 10.5%. The superiority over the historical control was also tested.

First Author, Publication Year, Country Design	N	Population	Country	Key Exclusions	Treatment Arms	Outcomes
				5 years. Current or past clinical evidence of cirrhosis		The historical control was treated with telaprevir plus peginterferon–Ribavirin.
Ferenci 2014[21] – PEARL-III (Genotype 1b) **Phase III double-blind RCTC**	419	noncirrhotic, treatment-naive patients between the ages of 18 and 70 with hcv genotype 1b (pearl –iii)	Europe And The United States	Hepatitis B surface antigen or anti–human immunodeficiency virus (HIV) antibodies Infection with any HCV genotype other than 1a Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. History of uncontrolled seizures, uncontrolled diabetes, active or suspected malignancy or history of in the past 5 years. Current or past clinical evidence of cirrhosis	HOLKIRA PAKA 12 WEEKS HOLKIRA PAKA + RBVB FOR 12 WEEKS	SVR12* Virologic failure Virologic relapse Adverse effects For SVR12, the non-inferiority to a historical control rate was tested (73%), with a ni margin of 10.5%. The superiority over the historical control was also tested. The non-inferiority between treatment arms was also tested (ni margin of 10.5%). The historical control was treated with telaprevir plus peginterferon–Ribavirin.
Ferenci 2014[21] – PEARL-IV (Genotype 1a) **Phase III double-blind RCTC**	305	noncirrhotic, treatment-naive patients between the ages of 18 and 70 with hcv genotype 1a	Canada, United States, United Kingdom	Hepatitis B surface antigen or anti–human immunodeficiency virus (HIV) antibodies Infection with any HCV genotype other than 1b Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. History of uncontrolled	HOLKIRA PAK 12 WEEKS HOLKIRA PAK + RBV FOR 12 WEEKS	SVR12* Virologic failure Virologic relapse Adverse effects *for SVR12, the non-inferiority to a historical control was tested (65%), with a ni margin of 10.5%. The superiority over the historical control was also tested. The non-inferiority between treatment arms was also tested (ni

First Author, Publication Year, Country Design	N	Population	Country	Key Exclusions	Treatment Arms	Outcomes
				seizures, uncontrolled diabetes, active or suspected malignancy or history of in the past 5 years. Current or past clinical evidence of cirrhosis		margin of 10.5%). The historical control was treated with telaprevir plus peginterferon–Ribavirin.
Poordad 2014[22] – TURQUOISE-II **Phase III open-label randomized trial**	380	treatment-naive and treatment experienced patients between the ages of 18 and 70 with hcv genotype 1a (69%) or 1b (31%) and child-pugh class a cirrhosis	Canada, United States, United Kingdom And Europe	Prior therapy with direct-acting antiviral agents (e.g., telaprevir and boceprevir) for the treatment of HCV infection Diagnosis of hepatocellular carcinoma	HOLKIRA PAKA FOR 12 WEEKS HOLKIRA PAKA FOR 24 WEEKS	*SVR12 Virologic failure Virologic relapse Adverse effects *for SVR12, the non-inferiority to a historical control rate (47%) was tested, with a ni margin of 10.5%. The superiority over the historical control was also tested. The historical control was treated with telaprevir plus peginterferon–Ribavirin.
Zeuzem 2014[20] – SAPPHIRE-II **Phase III double-blind, placebo-controlled RCT**	394	noncirrhotic, treatment-experienced patients between the ages of 18 and 70 with hcv genotype 1a (59%) or 1b (41%)	North America, Australia, Europe	Lack of response to prior triple therapy with peginterferon–ribavirin and a protease inhibitor. Hepatitis B surface antigen or anti–human immunodeficiency virus (HIV) antibodies Recent history of drug or alcohol abuse or a positive screening result for drugs or alcohol Specified concomitant medications, including those contraindicated for use with ribavirin and ritonavir	HOLKIRA PAKA + RBVB FOR 12 WEEKS PLACEBO FOR 12 WEEKS	*SVR12 Virologic failure Virologic relapse Normalization of alt Adverse effects *for SVR12, the non-inferiority to a historical control rate (65%) was tested, with a ni margin of 10.5%. The superiority over the historical control was also tested. The historical control rate was based upon patients who were

First Author, Publication Year, Country Design	N	Population	Country	Key Exclusions	Treatment Arms	Outcomes
				Advanced stage of fibrosis		previously treated with peginterferon–ribavirin and who received Retreatment with telaprevir and peginterferon–Ribavirin

ALT - Alanine transaminase HCV – Hepatitis C virus; HIV – Human immunodeficiency virus; NI – non-inferiority; RBV – Ribavirin; RCT – Randomized controlled trial; SVR12 – Sustained virologic response 12 weeks post-treatment;
A Holkira Pak - ABT-450/ritonavir/OBV (150/100/25 mg) co-formulated tablet once daily and Dasabuvir 250 mg twice daily
B 1,000 mg for weight < 75 kg or 1200mg for weight ≥ 75 kg.
C Double-blind to ribavirin treatment

Table 2B: Characteristics of Included Clinical Studies - Harvoni

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
Afdhal,[14] 2014, US	Open-label, randomized trial, Parallel Assignment, Treatment duration: 8 weeks or 12 weeks; follow up: 24-weeks after the end of therapy.	Patients with chronic HCV genotype 1 infection previously treated with PI or PR, n=440	ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 12 weeks, n=109; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 12 weeks, n=111; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 24 weeks, n=109; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 24 weeks, n=111	SVR12, SVR24 Safety
Afdhal,[12] 2014, US, France, Germany, Italy, Spain, Puerto Rico, and UK	Open-label, randomized trial, Parallel Assignment, Treatment duration: 12 weeks or 24 weeks; follow up: 12-weeks after the end of therapy.	Patients with chronic HCV genotype 1 infection (treatment naïve), n=865	ledipsavir 90 mg and sofosbuvir 400 mg orally one daily for 12 weeks, n=214; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 12 weeks, n=217; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 24 weeks, n=217; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 24 weeks, n=217	SVR12 Safety
Gane,[16] 2014, New Zealand	Open-label, included randomized and non-randomized arms, Treatment duration: 6 or 12 weeks; follow up: 24-weeks after	Patients with chronic HCV genotype 1 infection (treatment naïve) (n = 75), and patients who are previously treated (n = 38, with [n = 19] and without cirrhosis [n = 94])	<u>Treatment naïve patients:</u> ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=25 sofosbuvir 400 mg + GS-9669 500 mg once daily+ RBV (determined according to body	SVR12 Safety

Table 2B: Characteristics of Included Clinical Studies - Harvoni

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
	the end of therapy.		weight) orally in a divided daily dose for 12 weeks, n=25 FDC of sofosbuvir 400 mg and ledipsavir 90 mg + RBV (determined according to body weight) orally in a divided daily dose for 6 weeks, n=25 <u>Treatment experienced patients:</u> ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=9 sofosbuvir 400 mg and GS-9669 500 mg once daily+ RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=10 <u>prior null responders with cirrhosis:</u> FDC of sofosbuvir 400 mg and ledipsavir 90 mg orally once daily 12 weeks, n=10 FDC of sofosbuvir 400 mg and ledipsavir 90 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=9	
Kowdley,[13] 2014, US	Open-label, randomized trial, Parallel Assignment, Treatment duration: 8 weeks or 12 weeks; follow up: 12-weeks after the end of therapy.	Patients with chronic HCV genotype 1 infection (treatment naïve) without cirrhosis n=647	ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 8 weeks, n=215; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally twice daily for 8 weeks, n=216; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 12 weeks, n=216;	SVR 12 Safety
Lawitz,[23] 2014, US	Open-label, randomized	Patients with chronic HCV	<u>Treatment naïve patients:</u>	SVR 12, SVR 24

Table 2B: Characteristics of Included Clinical Studies - Harvoni

First Author, Publication Year, Country	Study design, length of follow-up	Patient characteristics, sample size	Interventions	Outcomes
	trial, Parallel Assignment, Treatment duration: 8 weeks or 12 weeks; follow up: 24-weeks after the end of therapy.	genotype 1 infection (treatment naïve) without cirrhosis, n=60, and patients previously treated with PI, n=40	ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 8 weeks, n=20; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 8 weeks, n=21; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 12 weeks, n=19; <u>treatment experienced patients:</u> ledipsavir 90 mg and sofosbuvir 400 mg orally once daily for 12 weeks, n=19; ledipsavir 90 mg and sofosbuvir 400 mg orally once daily + RBV (determined according to body weight) orally in a divided daily dose for 12 weeks, n=21	Safety
Osinusi,[17] 2014, US	Open-label, one group with 1 arm provided treatment, Treatment duration: 12 weeks, follow up: 12 weeks after the end of therapy	Patients with chronic HCV genotype 1 infection previously treated with DAA (sofosbuvir) + RBV, n = 14	FDC of sofosbuvir 400 mg + LBV 90 mg single combination tablet orally once daily for 12 weeks	SVR 12 Safety

DAA = direct-acting antiviral agents; FDC = fixed dose combination; HCV = chronic hepatitis C virus; LDV = ledipasvir; PI = protease inhibitors; PR = pegylated interferon alpha plus ribavirin; RBV = ribavirin; RCT = randomized controlled trial; SOF = sofosbuvir; SVR12 = sustained virological response 12 weeks after the end of treatment; SVR24 = sustained virological response 24 weeks after the end of treatment; UK = United Kingdom; US = United States.

APPENDIX 3: Critical Appraisal of Included Publications

Table 3A: Summary of Critical Appraisal of Included Clinical Studies – Holkira

First Author, Publication Year	Strengths	Limitations
Randomized Controlled Trial (SIGN-50 Checklist RCTs)[24]		
Andreone 2014[18] **PEARL-II**	• Appropriate and clearly focused research question • Assignment to treatment groups was randomized • Adequate concealment method used. • Similar at baseline with respect to age, ethnicity, BMI, HCV-RNA level, previous response to PR; however, there was a larger proportion of males in the Holkira Pak alone group. • Groups were treated similarly, with the exception of RBV, a treatment under study • Virologic outcomes were clearly defined • The dropout rate was approximately 4% and similar between arms • Analysis was based on the intention to treat principle.	Internal Validity Items from Checklist • Administration of RBV was open-label. While virologic outcomes are objectives, there is a potential bias for reporting of adverse effects. • There was no reporting of outcomes according to study location. Other Comments • The generalizability of the study results are limited by the exclusion of patients with hepatitis B or HIV co-infection, cirrhosis, and some other comborbidities such as diabetes • Patients who may not adhere to treatment due to issues related to drug and alcohol abuse were excluded, limiting the generalizability to these groups • Included only patients with genotype 1b infection, who were treatment experienced. • Non-inferiority of the treatment arms was in comparison to a historical control. o It is unclear of the characteristics of the patients in PEARL-II and the historical control were similar, whether the studies had similar inclusion/exclusion criteria, and if background medical care were similar • There was no rationale provided for the 10.5% non-inferiority margin that was used for the comparison to the historical control and between treatment arms.
Feld 2014[19] **SAPPHIRE-I**	• Appropriate and clearly focused research question • Assignment to treatment groups was randomized • Adequate concealment method used. • Participants and investigators were blind to treatment status • Similar at baseline with respect to age, ethnicity, BMI, HCV-RNA level, genotype distribuion; however, there was a larger proportion of males in the Holkira Pak group. • Groups were treated similarly, with the exception of the Holkira Pak, a treatment under study • Virologic outcomes were clearly defined • The dropout rate was approximately 2% and similar between arms • Analysis was based on the intention to treat principle.	Internal Validity Items from Checklist • There was no reporting of outcomes according to study location. Other Comments • While there was a placebo group, there was no reporting of efficacy outcomes for placebo or comparison made to the placebo group in terms of efficacy • The generalizability of the study results are limited by the exclusion of patients with hepatitis B or HIV co-infection, cirrhosis, and some other comborbidities such as diabetes • Patients who may not adhere to treatment due to issues related to drug and alcohol abuse were excluded, limiting the generalizability to these groups • Included only patients who were treatment naive • Non-inferiority of the treatment arms was in comparison to a historical control. o It is unclear of the characteristics of the patients in SAPPHIRE-I and the historical control were similar, whether the studies had similar inclusion/exclusion criteria, and if background medical care were similar • There was no rationale provided for the 10.5% non-inferiority margin that was used for the

First Author, Publication Year	Strengths	Limitations
		comparison to the historical control
Ferenci 2014[21] **PEARL-III**	• Appropriate and clearly focused research question • Assignment to treatment groups was randomized • Adequate concealment method used. • Participants and investigators were blind to treatment status • Similar at baseline with respect to age, ethnicity, BMI, HCV-RNA level; however, there was a larger proportion of males in the Holkira Pak combined with RBV group. • Groups were treated similarly, with the exception of RBV, a treatment under study • Virologic outcomes were clearly defined • The dropout rate was <1% and similar between arms • Analysis was based on the intention to treat principle.	Internal Validity Items from Checklist • There was no reporting of outcomes according to study location. Other Comments • The generalizability of the study results are limited by the exclusion of patients with hepatitis B or HIV co-infection, cirrhosis, and some other comorbidities such as diabetes • Patients who may not adhere to treatment due to issues related to drug and alcohol abuse were excluded, limiting the generalizability to these groups • Included only patients with genotype 1b infection and patients who were treatment naive. • Non-inferiority of the treatment arms was in comparison to a historical control. o It is unclear of the characteristics of the patients in PEARL-III and the historical control were similar, whether the studies had similar inclusion/exclusion criteria, and if background medical care were similar • There was no rationale provided for the 10.5% non-inferiority margin that was used for the comparison to the historical control and between treatment arms.
Ferenci 2014[21] **PEARL-IV**	• Appropriate and clearly focused research question • Assignment to treatment groups was randomized • Adequate concealment method used. • Participants and investigators were blind to treatment status • Similar at baseline with respect to age, ethnicity, BMI, HCV-RNA level; however, there was a larger proportion of males in the Holkira Pak combined with RBV group. • Groups were treated similarly, with the exception of RBV, a treatment under study • Virologic outcomes were clearly defined • The dropout rate was <5% • Analysis was based on the intention to treat principle.	Internal Validity Items from Checklist • There was no reporting of outcomes according to study location. • The dropout rate was higher in the RBV group (6% versus 0%) Other Comments • The generalizability of the study results are limited by the exclusion of patients with hepatitis B or HIV co-infection, cirrhosis, and some other comorbidities such as diabetes • Patients who may not adhere to treatment due to issues related to drug and alcohol abuse were excluded, limiting the generalizability to these groups • Included only patients with genotype 1a infection and patients who were treatment naive. • Non-inferiority of the treatment arms was in comparison to a historical control. o It is unclear of the characteristics of the patients in PEARL-IV and the historical control were similar, whether the studies had similar inclusion/exclusion criteria, and if background medical care were similar • There was no rationale provided for the 10.5% non-inferiority margin that was used for the comparison to the historical control and between treatment arms.
Poordad 2014[22] **TURQUOISE-II**	• Appropriate and clearly focused research question • Assignment to treatment groups was randomized • Adequate concealment method used.	Internal Validity Items from Checklist • There was no reporting of outcomes according to study location. • The study was unblinded with only a comparison between two durations of treatment, rather than an

First Author, Publication Year	Strengths	Limitations
	• Similar at baseline with respect to age, sex, ethnicity, BMI, HCV-RNA level, genotype, prior treatment experience. • Groups were treated similarly, with the exception of treatment duration • Virologic outcomes were clearly defined • The dropout rate was approximately 3% • Analysis was based on the intention to treat principle.	active or placebo comparator. Other Comments • The generalizability of the study results are limited by the exclusion of patients with hepatitis B or HIV co-infection, cirrhosis, and some other comorbidities such as diabetes • Patients who may not adhere to treatment due to issues related to drug and alcohol abuse were excluded, limiting the generalizability to these groups • Patients previously treated with DAAs were excluded • Non-inferiority of the treatment arms was in comparison to a historical control. o It is unclear of the characteristics of the patients in TURQUOISE-II and the historical control were similar, whether the studies had similar inclusion/exclusion criteria, and if background medical care were similar • There was no rationale provided for the 10.5% non-inferiority margin that was used for the comparison to the historical control
Zeuzem 2014[20] **SAPPHIRE-II**	• Appropriate and clearly focused research question • Assignment to treatment groups was randomized • Adequate concealment method used. • Participants and investigators were blind to treatment status • Similar at baseline with respect to age, sex, ethnicity, BMI, HCV-RNA level, previous treatment experience, genotype distribution; however, there was a larger proportion of North American patients in the Holkira Pak group. • Groups were treated similarly, with the exception of the Holkira Pak, a treatment under study • Virologic outcomes were clearly defined • The dropout rate was approximately 2% and similar between arms • Analysis was based on the intention to treat principle.	Internal Validity Items from Checklist • There was no reporting of outcomes according to study location. Other Comments • While there was a placebo group, there was no reporting of efficacy outcomes for placebo or comparison made to the placebo group in terms of efficacy • The generalizability of the study results are limited by the exclusion of patients with hepatitis B or HIV co-infection, cirrhosis, and some other comorbidities such as diabetes • Patients who may not adhere to treatment due to issues related to drug and alcohol abuse were excluded, limiting the generalizability to these groups • Included only patients who were treatment experienced and non-cirrhotic • Non-inferiority of the treatment arms was in comparison to a historical control. o It is unclear of the characteristics of the patients in SAPPHIRE-II and the historical control were similar, whether the studies had similar inclusion/exclusion criteria, and if background medical care were similar • There was no rationale provided for the 10.5% non-inferiority margin that was used for the comparison to the historical control

Table 3B: Summary of Critical Appraisal of Included Clinical Studies – Harvoni

First Author, Publication Year, Country	Strengths	Limitations
Afdhal,[14] 2014, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. An interactive Web and Response System for the randomization procedure • Post treatment HCV RNA results were blinded to the Investigator and Sponsor. • Number discontinued were reported • Choice of sample size was justified. • P-values provided	• No comparison was made between different treatment groups • SVR in each of the treatment groups were compared with an adjusted historical rate • Allocation was not described • Industry-sponsored study • Patients and investigators were not masked to treatment allocation • Lack of a control arms • Not clear if intent-to-treat analysis was used
Afdhal,[12] 2014, US, France, Germany, Italy, Spain, Puerto Rico, and UK	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. Interactive Web and Voice Response System used for the randomization procedure • Post treatment HCV RNA results were blinded to the Investigator and Sponsor. • Number discontinued or lost to follow up were reported • Choice of sample size was justified. • Intent-to-treat analysis was used • P-values provided	• SVR in each of the treatment groups were compared with an adjusted historical rate • No comparison was made between different treatment groups • Allocation was not described • Industry-sponsored study • Patients and investigators were not masked to treatment allocation • Lack of control arms
Gane,[16] 2014, New Zealand	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Some treatment arms were randomized but, open label study. Computer generated randomization sequence for the randomization procedure • Number discontinued or lost to follow up were reported	• No comparison was made between different treatment groups • Industry-sponsored study • Patients and investigators were not masked to treatment allocation • Lack of a control arms • Small sample size • No sample-size calculations were performed. • Not clear if intent-to-treat analysis was used • Not all patients were randomly assigned to treatments, as patients in some treatment arms were enrolled to receive treatment without randomization.

First Author, Publication Year, Country	Strengths	Limitations
Kowdley,[13] 2014, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. An interactive Web Response System for the randomization procedure • Post treatment HCV RNA results were blinded to the Investigator and Sponsor. • Number discontinued or lost to follow up were reported • Choice of sample size was justified. • Intent-to-treat analysis was used • P-values provided	• SVR in each of the treatment groups were compared with an adjusted historical rate • Allocation was not described • Industry-sponsored study • Patients and investigators were not masked to treatment allocation • Lack of control arms
Lawitz,[23] 2014, US	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • Randomized but open label study. Computerized random numbers used for the randomization procedure. • Number discontinued or lost to follow up were reported • Intent-to-treat analysis was used	• No comparison was made between different treatment groups • Allocation was not described • Industry-sponsored study • Patients and investigators were not masked to treatment allocation • Sample size was not powered to allow for comparison between groups • Lack of a control arms • Small sample size
Osinusi,[17] 2014, US	• Objectives and inclusion/exclusion criteria were stated • Patient characteristics, interventions, and outcomes were described • Number discontinued or lost to follow up were reported • Intent-to-treat analysis was used	• Lack of control arms • No randomization to treatment • No blinding of patients and investigators to treatment • Small sample size • Choice of sample size not justified • One treatment arm so no comparisons made, no p-values provided • Sponsored by manufacturer

HCV = chronic hepatitis C virus; RCT = randomized controlled trial; RNA = ribonucleic acid; SVR = sustained virological response; UK = United Kingdom; US = United States.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table 4A. Main Findings and Authors' Conclusions – Holkira

First Author, Publication Year	Main Study Findings		Authors' Conclusions
Andreone 2014[18] – PEARL-II	**Holkira Pak (n=91)**	**Holkira Pak + RBV (n=88)**	*"a 12-week regimen of ABT 450/ritonavir/ ombitasvir and dasabuvir[A] with or without RBV generally was well tolerated in pegIFN/RBV treatment-experienced, noncirrhotic, HCV genotype 1b–infected adults, as evidenced by the low rate of treatment discontinuation and serious AEs.* *ABT-450/ritonavir/ombitasvir and dasabuvir without RBV is sufficient to achieve optimal treatment of HCV genotype1b infection in this population." p.364*
Efficacy			
SVR12 – n (%)	91 (100) Superior to historical control Non-inferior to Holkira Pak + RBV	85 (96.6) Superior to historical control	
Virologic Failure – n (%)	0	0	
Post Treatment Relapse – n (%)	0	0	
Adverse Effects			
TEAEs – n (%)	74 (79.1)	72 (79.1)	
Discontinuation due to AEs – n (%)	0	2 (2.2)	
Fatigue – n (%)	15 (15.8)	29 (31.9)	
Headache – n (%)	22 (23.2)	22 (24.2)	
Nausea– n (%)	6 (6.3)	19 (20.9)	
Feld 2014[19] – SAPPHIRE-I	**Placebo (n=158)**	**Holkira Pak + RBV (n=473)**	
Efficacy			*"a multitargeted approach combining the direct-acting antiviral agents ABT-450/r–ombitasvir and dasabuvir[A] with ribavirin was associated with a high rate of sustained virologic response at post-treatment week 12, with a low rate of treatment discontinuation, among previously untreated patients with HCV genotype1 infection and no cirrhosis."p.1602*
SVR12 (Combined) – n (%)	-	455/473 (96.2) Superior to historical control	
SVR12 by Genotype			
Genotype 1a – n/n (%)	-	307/322 (95.3) Superior to historical control	
Genotype 1b – n/n (%)	-	148/151 (98.0) Superior to historical control	
Virologic Failure – n (%)	-	1 (0.2)	
Post Treatment Relapse – n (%)	-	7 (1.5)	
Normalization of ALT – n/n (%)	17/114 (14.9%)	352/363 (97%) p <0.001 compared with placebo	
Adverse Effects			
Any AEs – n (%)	116 (73.4)	414 (87.5)	
Discontinuation due to AEs – n (%)	1 (0.6)	3 (0.6)	
Fatigue – n (%)	45 (28.5)	164 (34.7)	
Headache – n (%)	42 (26.6)	156 (33.0)	
Nausea – n (%)	21 (13.3)	112 (23.7)	
Ferenci 2014[21] – PEARL-III (Genotype 1b)	**Holkira Pak (n=209)**	**Holkira Pak + RBV (n=210)**	
Efficacy			*"previously untreated patients with HCV genotype 1a or 1b*
SVR12 – n (%)	207 (99.0)	209 (99.5)	

First Author, Publication Year	Main Study Findings		Authors' Conclusions
	Superior to historical control Non-inferior to Holkira Pak + RBV	Superior to historical control	*infection and no cirrhosis who received ABT-450/r–ombitasvir and dasabuvir[A] with or without ribavirin had high sustained-virologic-response rates that were superior to the historical response rate with peginterferon–ribavirin plus telaprevir. …ribavirin did not improve the response in patients with genotype 1b infection…"p.1991*
Virologic Failure – n (%)	0	1 (0.5)	
Virologic Relapse – n (%)	0	0	
Adverse Effects			
Any AEs – n (%)	140 (67.0)	168 (80.0)	
Headache – n (%)	49 (23.4)	51 (24.3)	
Fatigue – n (%)	48 (23.0)	45 (21.4)	
Nausea – n(%)	9 (4.3)	23 (11.0)	
Ferenci 2014[21] – PEARL-IV (Genotype 1a)	**Holkira Pak (n=205)**	**Holkira Pak + RBV (n=100)**	
Efficacy			*"previously untreated patients with HCV genotype 1a or 1b infection and no cirrhosis who received ABT-450/r–ombitasvir and dasabuvir[A] with or without ribavirin had high sustained-virologic-response rates that were superior to the historical response rate with peginterferon–ribavirin plus telaprevir. Although ribavirin did not improve the response in patients with genotype 1b infection, our findings suggest that ribavirin confers an additional benefit for patients with genotype 1a infection."p.1991*
SVR12 – n (%)	185 (90.2) Superior to historical control Non-inferior to Holkira Pak + RBV	97 (97.0) Superior to historical control	
Virologic Failure – n (%)	6 (2.9)	1 (1.0)	
Virologic Relapse – n (%)	10/194 (5.2)	1/98 (1.0)	
Adverse Effects			
Any AEs – n (%)	169 (82.4)	92 (92.0)	
Headache – n (%)	58 (28.3)	25 (25.0)	
Fatigue – n (%)	72 (35.1)	46 (46.0)	
Nausea – n(%)	28 (13.7)	21 (21.0)	
Poordad 2014[22] – TURQUOISE-II	**Holkira Pak + RBV for 12 weeks (n=208)**	**Holkira Pak + RBV for 24 weeks (n=172)**	
Efficacy			*"this multitargeted approach combining ritonavir-enhanced ABT-450 with ombitasvir, dasabuvir[A], and ribavirin resulted in rates of sustained virologic response at post-treatment week 12 of 92% with a 12-week regimen and 96% with a 24-week regimen, with a low rate of treatment discontinuation, among both previously untreated and previously treated patients with HCV genotype 1 infection and compensated cirrhosis, a group at risk for liver-related illness and death." p.1982*
SVR12 (Combined) – n (%)	191 (91.8) Superior to historical control	165 (95.9) Superior to historical control p=0.09 compared to 12 week regimen	
SVR12 by Genotype			
Genotype 1a – n/n (%)	124/140 (88.6)	114/121 (94.2)	
Genotype 1b – n/n (%)	67/68 (98.5)	51/51 (100)	
SVR12 by Prior Response			
No Prior Treatment– n/n (%)	81/86 (94.2)	70/74 (94.6)	
Relapse – n/n (%)	28/29 (96.6)	59/62 (95.2)	
Partial Response – n/n (%)	17/18 (94.4)	13/13 (100)	
Null Response – n/n (%)	65/75 (86.7)	23/23 (100)	
Virologic Failure – n (%)	1/208 (0.5%)	3/172 (1.7%)	
Virologic Relapse – n (%)	12/203 (5.9%)	1/164 (0.6%)	
Adverse Effects			
Any AEs – n (%)	191 (91.8)	156 (90.7)	
Discontinuation due to AEs	4 (1.9)	4 (2.3)	

First Author, Publication Year	Main Study Findings		Authors' Conclusions
– n (%)			
Fatigue – n (%)	68 (32.7)	80 (46.5)	
Headache – n (%)	58 (27.9)	53 (30.8)	
Nausea – n (%)	37 (17.8)	35 (20.3)	
Zeuzem 2014[20] – SAPPHIRE-II	**Placebo (n=97)**	**Holkira Pak + RBV (n=297)**	
Efficacy			*"an all-oral combination regimen of ABT-450/r, ombitasvir, and dasabuvir[A] with ribavirin resulted in rates of sustained virologic response at post-treatment week 12 of more than 95%, regardless of HCV genotype (1a or 1b) and with low rates of treatment discontinuation, in previously treated patients with HCV genotype 1infection and no cirrhosis, including those with a prior null response."p.1613*
SVR12 (Combined) – n (%)	-	287 (96.3) Superior to historical control	
SVR12 by Genotype			
Genotype 1a – n/n (%)	-	166/173 (96.0)	
Genotype 1b – n/n (%)	-	119/123 (96.7)	
SVR12 by Prior Response			
Relapse – n/n (%)	-	82/86 (95.3)	
Partial Response – n/n (%)	-	65/65 (100)	
Null Response – n/n (%)	-	139/146 (95.2)	
Virologic Failure – n (%)	-	0	
Virologic Relapse – n (%)	-	7/293 (2.4)	
Normalization of ALT – n (%)	10/78 (12.8)	217/224 (96.9) p <0.001 compared with placebo	
Adverse Effects			
Any AEs – n (%)	80 (82.5)	271 (91.2)	
Discontinuation due to AEs – n (%)	0	3 (1.0)	
Fatigue – n (%)	22 (22.7)	99 (33.3)	
Headache – n (%)	34 (35.1)	108 (36.4)	
Nausea – n (%)	17 (17.5)	60 (20.2)	

AEs – Adverse effects; ALT - Alanine transaminase; HCV – Hepatitis C virus; HIV – Human immunodeficiency virus; NI – non-inferiority; RBV – Ribavirin; RCT – Randomized controlled trial; SVR12 – Sustained virologic response 12 weeks post-treatment; TEAE – Treatment emergent adverse effect

A Holkira Pak - ABT-450/ritonavir/ombitasvir (150/100/25 mg) co-formulated tablet once daily and Dasabuvir 250 mg twice daily

Table 4B. Main Findings and Authors' Conclusions – Harvoni

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Afdhal,[14] 2014, US</td><td>
Main Findings:
<table>
<tr><th>Outcome</th><th>12-Wk Harvoni (N=109)</th><th>12-Wk Harvoni + RBV (N=111)</th><th>24-Wk Harvoni (N=109)</th><th>24-Wk Harvoni + RBV (N=111)</th></tr>
<tr><td colspan="5">Efficacy</td></tr>
<tr><td>SVR12, n (%)</td><td>102 (94)</td><td>107 (96)</td><td>108 (99)</td><td>110 (99)</td></tr>
<tr><td>SVR24, n (%)</td><td>102 (94)</td><td>107 (96)</td><td>108 (99)</td><td>110 (99)</td></tr>
<tr><td colspan="5">Safety</td></tr>
<tr><td>SAE, n (%)</td><td>0</td><td>0</td><td>6 (6)</td><td>3 (3)</td></tr>
<tr><td>Discontinued treatment due to AE, n (%)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Any AE, n (%)</td><td>73 (67)</td><td>96 (86)</td><td>88 (81)</td><td>100 (90)</td></tr>
<tr><td>Anemia, n (%)</td><td>0</td><td>9 (8)</td><td>1 (1)</td><td>12 (11)</td></tr>
<tr><td>Rash, n (%)</td><td>2 (2)</td><td>11 (10)</td><td>6 (6)</td><td>16 (14)</td></tr>
<tr><td>Depression, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
</table>
Authors' Conclusion:
Once-daily of FDC of Harvoni resulted in high rates of SVR in patients with HCV genotype 1 infection who had not had a SVR to prior interferon based treatment.
</td></tr>
<tr><td>Afdhal,[12] 2014, US, France, Germany, Italy, Spain, Puerto Rico, and UK</td><td>
Main Findings:
<table>
<tr><th>Outcome</th><th>12-Wk Harvoni (N=214)</th><th>12-Wk Harvoni + RBV (N=217)</th><th>24-Wk Harvoni (N=217)</th><th>24-Wk Harvoni + RBV (N=217)</th></tr>
<tr><td colspan="5">Efficacy</td></tr>
<tr><td>SVR12, n (%)</td><td>211 (99)</td><td>211 (97)</td><td>212 (98)</td><td>215 (99)</td></tr>
<tr><td colspan="5">Safety</td></tr>
<tr><td>SAE, n (%)</td><td>1 (<1)</td><td>7 (3)</td><td>18 (8)</td><td>7 (3)</td></tr>
<tr><td>Discontinued treatment due to AE, n (%)</td><td>0</td><td>0</td><td>4 (2)</td><td>6 (3)</td></tr>
<tr><td>Any AE, n (%)</td><td>169 (79)</td><td>185 (85)</td><td>178 (82)</td><td>200 (92)</td></tr>
<tr><td>Anemia, n (%)</td><td>0</td><td>25 (12)</td><td>0</td><td>22 (10)</td></tr>
<tr><td>Rash, n (%)</td><td>16 (7)</td><td>21 (10)</td><td>16 (7)</td><td>27 (12)</td></tr>
<tr><td>Depression, n (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
</table>
</td></tr>
</table>

Authors' Conclusion:
Once-daily of FDC of Harvoni with or without RBV for 12 or 24 weeks was highly effective in patients with HCV genotype 1 infection who are treatment naïve

Gane,[16] 2014, New Zealand

Main Findings:

Outcome	treatment-naive patients			patients previously treated with PR			
	12-Wk ledipsavir + sofosbuvir + RBV (N=25)	12 WK sofosbuvir + GS-9669 + RBV (N=25)	6-Wk ledipsavir and sofosbuvir + RBV (N=25)	12-Wk ledipsavir + sofosbuvir + RBV (N=9)	12 Weeks sofosbuvir + GS-9669 + RBV (N=10)	12-Wk ledipsavir and sofosbuvir cirrhotic patients (N=10)	12-Wk ledipsavir and sofosbuvir + RBV cirrhotic patients (N=9)
Efficacy							
SVR12, n (%)	25 (100)	23 (92)	17 (68)	9 (100)	10 (100)	7 (70)	9 (100)
Safety							
SAE, n (%)	NR	NR	NR	NR	NR	NR	NR
Discontinued treatment due to AE, n (%)	1 (4)	0	0	0	0	0	0
Any AE, n (%)	24 (96)	25 (100)	22 (88)	9 (100)	10 (100)	7 (70)	8 (89)
Anemia, n (%)	NR	NR	NR	NR	NR	NR	NR
Rash, n (%)	4 (16)	5 (20)	3 (12)	1 (11)	1 (10)	0	0
Depression, n (%)	4 (16)	0	0	2 (22)	1 (10)	0	1 (11)

Authors' Conclusion:
The combination of ledipsavir and sofosbuvir is highly effective in patients with HCV genotype 1 infection who are treatment naïve or did not respond to previous treatment

Kowdley,[13] 2014, US

Main Findings:

Outcome	8-Wk Harvoni (N=215)	8-Wk Harvoni + RBV (N=216)	12-Wk Harvoni (N=216)
Efficacy			
SVR12, n (%)	202 (94)	201 (93)	206 (95)
Safety			
SAE, n (%)	4 (2)	1 (<1)	5 (2)
Discontinued treatment due to AE, n (%)	0	1 (<1)	2 (1)
Any AE, n (%)	145 (67)	165 (76)	149 (69)
Anemia, n (%)	2 (1)	17 (8)	2 (1)
Rash, n (%)	3 (1)	19 (9)	5 (2)

	Depression, n (%) | NR | NR | NR **Authors' Conclusion:** Once-daily of FDC of Harvoni for 8 weeks was associated with a high rate of SVR among treatment naïve patients with HCV genotype 1 infection without cirrhosis. The inclusion of ribavirin in the regimen and the extension of the duration of treatment to 12 weeks were not associated with additional benefit.
Lawitz,[23] 2014, US	**Main Findings:** **Outcome** | **treatment-naive patients** | | | **patients previously treated with PI** | 8-Wk Harvoni (N=20) | 8-Wk Harvoni + RBV (N=21) | 12-Wk Harvoni (N=19) | 12-Wk Harvoni (N=19) | 12-Wk Harvoni + RBV (N=21 Efficacy | | | | | SVR12, n (%) | 19 (95) | 21 (100) | 18 (95) | 18 (95) | 21 (100) SVR24, n (%) | 19 (95) | 21 (100) | 18 (95) | 18 (95) | 21 (100) Safety | | | | | SAE, n (%) | 0 | 1 (5) | 1 (5) | 1 (5) | 1 (5) Discontinued treatment due to AE, n (%) | 0 | 0 | 0 | 0 | 0 Any AE, n (%) | 9 (45) | 12 (57) | 8 (42) | 7 (37) | 12 (57) Anemia, n (%) | NR | NR | NR | NR | NR Rash, n (%) | NR | NR | NR | NR | NR Depression, n (%) | NR | NR | NR | NR | NR **Authors' Conclusion:** Once-daily of FDC of Harvoni with or without RBV has the potential to cure most patients with genotype-1 HCV, regardless of the presence of compensated cirrhosis or treatment history.
Osinusi,[17] 2014, US	**Main Findings** **Outcome** | **Patients previously treated with sofosbuvir + RBV** | 12 Wk ledipsavir and sofosbuvir (n = 14) **Efficacy** SVR12, n (%) | 14 (100) **Safety** SAE, n (%) | 0 (0) Discontinued treatment due to AE, n (%) | 0 (0) Any AE, n (%) | NR Anemia, n (%) | NR Rash, n (%) | 1 (7) Depression, n (%) | NR

	Authors' Conclusion: In patients who failed treatment or relapsed after treatment with sofosbuvir plus RBV, subsequent treatment with a FDC of LBV and sofosbuvir resulted in SVR12 rates of 100% in a small group of patients with prevalent advanced liver disease.

AE = adverse event; DAA = direct-acting antiviral agents; FDC = fixed dose combination; HCV = chronic hepatitis C virus; ledipsavir = ledipasvir; NR = not reported; PI = protease inhibitors; RBV = ribavirin; RCT = randomized controlled trial; SAE = serious adverse event; sofosbuvir = sofosbuvir; SVR = sustained virological response; SVR12 = sustained virological response 12 weeks after the end of treatment; SVR24 = sustained virological response 24 weeks after the end of treatment; UK = United Kingdom; US = United States.

APPENDIX 5: Additional References of Potential Interest

Holkira:

Pooled Analyses

1. Colombo M, Weiland O, Cohen DE, DuFour J-F, Reynaert H, Diago M, et al. SVR12 rate of 98.6% in 992 HCV genotype 1b-infected patients treated with ABT-450/r/ombitasvir and dasabuvir with or without ribavirin [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

   Objective: The multi-targeted 3 direct-acting antiviral (3D) regimen of ombitasvir (an NS5A inhibitor), ABT-450 (an HCV NS3/4A protease inhibitor identified by AbbVie and Enanta, dosed with ritonavir [r]), and dasabuvir (a non-nucleoside NS5B RNA polymerase inhibitor) has demonstrated high SVR rates in patients infected with HCV genotype (GT) 1. We report the efficacy of the 3D regimen with or without ribavirin (RBV) in HCV GT1b-infected patients across 5 phase 3 clinical trials, including patients with prior pegIFN/RBV (PR) null response and those with cirrhosis. Methods: Patients treated in the PEARL-II, PEARL-III, SAPPHIRE-I, SAPPHIRE-II or TURQUOISE- II trials received 12 or 24 wks of coformulated ombitasvir/ ABT-450/r and dasabuvir with or without weight-based RBV. Intent-to-treat SVR rates 12 wks post-treatment (SVR12) were assessed. Results: 992 patients infected with HCV GT1b were enrolled in the USA (N=214), Europe (N=582), and the rest of the world (N=196). Among patients without cirrhosis who received 3D alone, 99.3% (299/301) achieved SVR12. In patients who received 3D+RBV for 12 or 24 wks, 98.3% (679/691) achieved SVR12, including 67/68 (98.5%) with cirrhosis treated for 12 wks. All treatment-experienced patients without cirrhosis achieved SVR12 (91/91) after 12 weeks of 3D alone. Similarly, all patients with both cirrhosis and prior PR null response achieved SVR12 after treatment with 3D+RBV for 12 or 24 wks. No patient receiving 3D alone experienced virologic failure or relapse by post-treatment wk 12; on-treatment failure or relapse occurred in 0.1% (1/691) and 0.6% (4/684) of patients receiving 3D+RBV, respectively. Serious AEs occurred in 2.3% (23/995+) of patients overall; 0.5% (5/995) discontinued due to AEs, all of whom received 3D+RBV. Conclusions: The 12-wk 3D regimen with or without RBV achieved optimal efficacy in all HCV GT1b-infected patients, including historically difficult to cure subgroups with prior PR null response and/or cirrhosis. The addition of RBV to the 3D regimen did not provide additional benefit in patients without cirrhosis, nor did longer treatment duration in patients with cirrhosis treated with 3D+RBV. +995 patients were enrolled; 992 were included in efficacy analyses. (Table Presented)

2. Everson GT, Dusheiko G, Coakley E, Shafran SD, Zoulim F, Diago M, et al. Integrated efficacy analysis of four phase 3 studies in HCV genotype 1a-infected patients treated with ABT-450/r/ombitasvir and dasabuvir with or without ribavirin [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

   Objective: The interferon-free, all-oral, 3 direct-acting antiviral (3D) regimen of coformulated ABT-450 (an HCV NS3/4A protease inhibitor identified by AbbVie and Enanta, dosed with ritonavir [r]) and ombitasvir (an NS5A inhibitor) with dasabuvir (a non-nucleoside NS5B RNA polymerase inhibitor) achieves high rates of sustained virologic response (SVR) in patients (pts) infected with HCV genotype (GT) 1. We report the pooled data from four phase 3 clinical trials assessing the SVR12 rates of the 3D regimen with or without ribavirin (RBV) in treatment-naive and prior pegIFN/RBV (PR)-experienced pts with or without cirrhosis infected with HCV GT1a. Methods: Patients infected with HCV GT1a in the PEARL-IV, SAPPHIRE-I, SAPPHIRE-II, or TURQUOISE-II trials received 12 weeks (including pts with cirrhosis) or 24 weeks (only pts with cirrhosis) of 3D with weightbased RBV (including pts with cirrhosis) or without RBV (only treatment-naive pts without cirrhosis). SVR12 rates were based on intent-to-treat population. Results: Among the 1060 HCV GT1a-infected pts, 632

were from the United States, 295 from Europe, and 133 from the rest of the world. In pts without cirrhosis, 12 weeks of 3D+RBV yielded similarly high SVR12 rates in treatment naive and PR-experienced groups (Table). SVR12 rates were higher in treatment-naive pts without cirrhosis receiving 3D+RBV (95.7%) compared to 3D alone (90.2%). High SVR12 rates were observed with both 12 and 24 week treatments in pts with cirrhosis, however, in GT1a-infected pts with cirrhosis and a prior PR null response a higher SVR12 rate was observed with longer treatment duration. Among pts receiving 3D+RBV, the rates of on-treatment virologic failure and relapse by post-treatment week 12 were low, 0.7% (6/856) and 2.9% (24/830), respectively. In pts without cirrhosis receiving 3D alone, 2.9% (6/204) had on-treatment virologic failure, and 5.2% (10/193) relapsed. Serious adverse events and discontinuations due to adverse events occurred in 2.8% (30/1060) and 1.2% (13/1060) of pts, respectively. Conclusions: In HCV GT1a-infected pts, the 3D+RBV regimen achieved high SVR12 rates, including historically difficult to cure subgroups of pts with prior PR null response and/or cirrhosis. In treatment-naive pts without cirrhosis the addition of RBV to 3D improved SVR12 rates. GT1a-infected pts with cirrhosis and a prior PR null response may benefit from longer treatment duration. (Table presented)

3. Flamm SL, Gane EJ, DuFour J-F, Rustgi V, Bain VG, Crawford DH, et al. Safety of ABT-450/r/ombitasvir + dasabuvir with or without ribavirin in HCV genotype 1-infected patients >65 years of age: Results from phase 2 and 3 trials [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

   Purpose: Aging is associated with accelerated fibrosis progression in chronic hepatitis C, yet treatment with interferon-based therapies is difficult for older patients to tolerate. In adults with chronic GT1 hepatitis C virus (HCV) infection, similar SVR12 rates (97.1% vs. 95.9%) were observed in patients >65 vs. <65 years of age in phase 3 trials of co-formulated ABT- 450/r/ombitasvir and dasabuvir (3D regimen) with or without ribavirin (RBV). We evaluated safety in patients >65 years of age across phase 2 and 3 trials of 3D+RBV. Methods: HCV GT1 infected treatment-naive, treatment-experienced, cirrhotic and non-cirrhotic patients were enrolled in phase 3 trials (SAPPHIRE- I or -II, PEARL-II, -III, or -IV, TURQUOISE-II) or phase 2 (AVIATOR, M14-103) trials of 3D+RBV and received at least one dose of study drug at the following or higher dosages: ABT-450 150mg once daily, ritonavir 100mg once daily, ombitasvir 25mg QD, and dasabuvir 250mg twice daily, with or without weight-based RBV. Patients from placebo groups in the SAPPHIRE trials were also included. The incidence of treatment-emergent adverse events (AEs) and treatment discontinuation rates was determined for patients <65 and >65 years of age. Results: In the active treatment groups, there were 214 patients who were >65 year old at the time of treatment initiation; 49 (22.9%) had compensated cirrhosis compared with 331 (13.7%) of the <65 group. There was no significant interaction between treatment and age across the frequent safety outcomes, regardless of inclusion of RBV (Table), with the exception of higher rates of anemia and RBV dose modification in the elderly group compared with the younger group. The overall rate of discontinuation due to an AE was low for patients in both age categories receiving active drug; placebo results are also provided. Conclusions: The interferon-free combination of ABT-450/ombitasvir and dasabuvir with or without ribavirin was safe and effective in patients >65 years of age, including those with cirrhosis. (Table Presented)

4. Fried MW, Di Bisceglie AM, Vierling JM, Gane EJ, Nevens F, Strasser SI, et al. Safety of ABT-450/r/ombitasvir + dasabuvir with or without ribavirin in HCV genotype 1-infected patients: Results from phase 2 and phase 3 trials [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

   Purpose: Interferon-based therapies are associated with significant toxicity and adverse events. Adults with chronic GT1 hepatitis C virus infection, including those with compensated cirrhosis, achieved high SVR12 rates in phase 3 trials of the interferon-free 3D regimen of ABT-450 (dosed with ritonavir, ABT-450/r), ombitasvir, and dasabuvir, with or without ribavirin (RBV). We evaluated

safety across phase 2 and phase 3 trials of 3D+RBV. Methods: Treatment-naive, treatment-experienced, cirrhotic and non-cirrhotic patients were enrolled in phase 2 or phase 3 trials of 3D+RBV and received at least one dose of placebo, or study drug at the following or higher dosages: ABT-450 150mg once daily, ritonavir 100mg once daily, ombitasvir 25mg QD, and dasabuvir 250mg twice daily, +weight-based RBV. Adverse event (AE) assessment and clinical laboratory testing occurred at study visits during treatment and follow-up for the 3D+RBV, 3D, and placebo arms. Results: Of 2887 patients (3D+RBV: N=2044; 3D: N=588; placebo: N=255), most experienced at least 1 (predominantly mild) treatment-emergent AE (Table). The overall rate of discontinuation due to an AE was low in the active treatment arms (27/2632, 1.0%). AEs occurring in >20% of patients the 3D+RBV, 3D, or placebo groups, respectively, were fatigue (32.3%, 25.7%, and 26.3%) and headache (28.9%, 24.5%, and 29.8%). Transient bilirubin elevations (predominantly indirect), due to the known effect of ABT-450 inhibition on bilirubin transporters, typically peaked by week 1, were not associated with ALT elevations and did not result in any treatment discontinuations. Infrequent asymptomatic ALT elevations were transient, typically occurred by week 1-2 and declined without study drug interruption. Concurrent systemic estrogen use was the main risk factor for ALT elevations. Hemoglobin declines to <10g/dL were infrequent, related to RBV use, and manageable by RBV dose reduction. Less than 0.5% of patients received erythropoietin or red blood cell transfusion. Conclusions: The combination of ABT-450/r/ombitasvir and dasabuvir with or without RBV is well tolerated in a broad and diverse patient population. (Table Presented)

5. Jacobson IM, DuFour J-F, Enejosa J, De Knegt RJ, Ferenci P, Reynaert H, et al. SVR12 rate of 95.7% in 209 HCV genotype 1-infected null responders treated with ABT-450/r/ombitasvir and dasabuvir with or without ribavirin [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

   Purpose: The multi-targeted all-oral 3 direct-acting antiviral (3D) regimen of ABT-450 (identified by AbbVie and Enanta and dosed with ritonavir [r]), ombitasvir, and dasabuvir has demonstrated high SVR rates in patients infected with HCV genotype (GT) 1. We assessed the efficacy and safety of the 3D regimen with or without ribavirin (RBV) in HCV GT1-infected patients who were null responders to prior treatment with pegylated interferon/RBV (<2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 or <1 $\log_{10}$ IU/mL reduction at week 4). Methods: Non-cirrhotic null responders who were enrolled in phase 3 trials of 3D+RBV (SAPPHIRE-II or PEARL-II) and received at least one dose of study drug (co-formulated ABT- 450/r/ombitasvir 25mg/150mg/100mg once daily, dasabuvir 250mg twice daily, with or without weight-based RBV) were included in the analysis. SVR12 rates, incidence of adverse events (AEs) and treatment discontinuation due to AE were determined. Results: 209 prior null responders were included; 122 (58.4%) were male, 186 (89.0%) were white, 110 (52.6%) were <55 years of age. SVR12 was achieved in 200/209 patients (95.7%, table), and similar SVR12 rates were observed in GT1a and GT1b null responders. All 32 GT1b-infected patients who received 3D without RBV achieved SVR12 (100%). AEs occurring in >10% of patients were headache, fatigue, nausea, asthenia, insomnia, diarrhea and pruritus. Most AEs were mild, and the rates of SAEs and study drug discontinuations due to AEs were low (3.3% and 1.0% overall, respectively). Conclusions: In two phase 3 trials, treatment with a potent combination of direct acting antivirals (3D) with or without RBV resulted in high SVR12 rates in patients who were prior pegIFN/RBV null responders, historically a difficult to treat population. Rates were similar regardless of 1a or 1b subgenotype, and there were few SAEs or study drug discontinuations due to AEs. (Table Presented)

6. Jensen DM, Baykal T, Lawitz E, Feld JJ, Angarano G, Jayakumar S, et al. Adverse event profile of the interferon-free all-oral abt-450/r/ombitasvir, dasabuvir, and ribavirin regimen in HCV patients [abstract]. J Gastroenterol Hepatol. 2014;29(Suppl 2):155. (Presented at Australian Gastroenterology Week 2014 Broadbeach; 2014 Oct 22-24; QLD Australia).

   Background: Phase 3 trials with the 3 direct-acting antiviral (3D) regimen of ABT-450/ritonavir (identified by AbbVie and Enanta), ombitasvir (formerly ABT-267), and dasabuvir (formerly ABT-333)

with ribavirin (RBV) in non-cirrhotic, treatment-naive (SAPPHIRE-I) and pegIFN/RBV-experienced (SAPPHIRE-II) HCV genotype 1-infected patients achieved 12-week post-treatment sustained virologic response (SVR12) rates of 96.2% and 96.3%. Pooled safety data from these trials are reported. Methods: Patients were randomized 3:1 to the 3D regimen with ribavirin or matching placebos during 12-week double-blind periods. Adverse assessment and clinical laboratory testing were performed at each treatment visit. Results: Overall, 89.0% of patients receiving 3D + RBV and 76.9% of patients receiving placebo reported adverse events. Most AEs were mild or moderate in severity. 3/770 (0.4%) patients receiving 3D + RBV and no patients receiving placebo experienced a serious AE having a reasonable possibility of being related to study drug. Differences in the proportion of patients experiencing AEs were small between prior treatment-naive and treatment-experienced patients and between those receiving 3D + RBV and placebo. Rates of study drug discontinuation due to AEs were similar and low in the 2 treatment groups (0.4-0.8%). Conclusions: The 3D + RBV regimen demonstrated a favorable AE profile as evidenced by low rates of study drug discontinuation, drugrelated serious AEs, and generally mild AEs. Previous exposure to treatment did not influence the safety profile

7. Lalezari JP, Pruitt R, Luo Y, Aspinall RJ, Gaeta GB, Olszok I, et al. Safety of ABT-450/r/ombitasvir + dasabuvir with or without ribavirin in HCV genotype 1-infected patients: Results from PEARL II, PEARL III, and PEARL IV [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

   Introduction: ABT-450 is an HCV NS3/4A protease inhibitor dosed with ritonavir (r), identified by AbbVie and Enanta. Ombitasvir (formerly ABT-267) and dasabuvir (formerly ABT- 333) inhibit NS5A and NS5B, respectively. The phase 3 trials PEARL II, PEARL III, and PEARL IV examined the efficacy and safety of 12 week regimens of co-formulated ABT-450/r/ ombitasvir + dasabuvir (3D) with or without ribavirin (RBV) in non-cirrhotic patients with HCV genotype (GT) 1a and 1b infection. Safety outcomes in patients receiving RBV-containing and RBV-free regimens in these trials are reported. Methods: GT1b-infected treatment-experienced patients (PEARL II), GT1b-infected treatment-naive patients (PEARL III), and GT1a-infected treatment-naive patients (PEARL IV) were randomized to co-formulated ABT-450/r/ombitasvir (150mg/100mg/25mg QD) + dasabuvir (250mg BID) with weight-based RBV or placebo/no RBV. Adverse event (AE) and clinical laboratory assessment occurred at study visits during treatment and follow- up for all patients who received at least one dose of study drug. Results: In PEARL II, PEARL III, and PEARL IV, respectively, 186, 419, and 305 patients were randomized and received at least one dose of study drug. Collectively, 401 patients received 3D+RBV and 509 received 3D. Treatment-emergent AEs and laboratory values of note are in the Table. In both the 3D+RBV and 3D groups, the majority of AEs were mild. AEs occurring in >20% of patients in both the 3D+RBV and 3D groups were fatigue (29.9% and 26.5%) and headache (24.4% and 25.3%). RBV dose modifications were made following an AE in 8.5% of patients receiving 3D+RBV, all of whom achieved SVR12. The rate of discontinuation due to AEs was 0.5% or less among patients treated with 3D+RBV or 3D. Conclusions: In the PEARL II, PEARL III, and PEARL IV trials, 3D was well tolerated either with or without RBV. Comparable low rates of discontinuation were observed in patients receiving 3D and 3D+RBV. Clinically significant hemoglobin reductions and bilirubin elevations were infrequent and not treatment-limiting. (Table Presented)

8. Maieron A, Puoti M, Enejosa JV, Andreone P, Ari ZB, Norkrans G, et al. SVR12 of 99% achieved with a ribavirin-free regimen ABT-450/R/ombitasvir and dasabuvir in HCV genotype 1b-infected patients [abstract]. J Gastroenterol Hepatol. 2014;29(Suppl 2):156. (Presented at Australian Gastroenterology Week 2014 Broadbeach; 2014 Oct 22-24; QLD Australia).

   Objective: ABT-450 is an HCV NS3/4A protease inhibitor (identified by AbbVie and Enanta) dosed with ritonavir (r). Ombitasvir (formerly ABT- 267) is an NS5A inhibitor, and dasabuvir (formerly ABT-333) is a nonnucleoside NS5B RNA polymerase inhibitor. We report the sustained virologic response 12 weeks post-treatment (SVR12) achieved in HCV genotype 1b-infected patients after treatment

with these 3 direct-acting antivirals (3D regimen) with or without ribavirin (RBV). Methods: Five hundred ninety-nine treatment-naive and prior pegIFN/ RBV-experienced HCV genotype 1b-infected patients without cirrhosis were enrolled and received study drugs in the PEARL-II and PEARL-III randomized phase 3 studies. Patients were randomized 1:1 to co-formulated ABT-450/r/ombitasvir (150 mg/100 mg/25 mg once daily) and dasabuvir (250 mg twice daily) with or without weight-based RBV (1000-1200 mg daily). Results: The combined SVR12 rate from PEARL-II and PEARL-III was 99.3% in 301 patients who received 3D regimen without RBV vs. 98.7% in 298 patients who received 3D + RBV. Two patients (0.7%) receiving 3D without RBV did not achieve SVR12, both due to missing week 12 posttreatment follow-up. Four 3D + RBV patients did not achieve SVR12: 1 (0.3%) due to virologic breakthrough, 1 (0.3%) due to missing SVR12 data, and 2 (0.7%) due to study drug discontinuation for adverse events. SVR12 rates did not differ between 3D and 3D + RBV by baseline factors including IL28B genotype, sex, age, race, ethnicity, BMI, fibrosis stage, and HCV RNA viral load. No patients receiving 3D and 0.7% of patients receiving 3D + RBV discontinued due to adverse events. Conclusions: Irrespective of previous pegIFN/RBV treatment response and other baseline factors, HCV genotype 1b-infected patients achieved high SVR rates after 12 weeks of 3D without RBV. Overall, only 1 (3D + RBV) of 599 (0.2%) patients experienced virologic breakthrough and none experienced relapse. Both regimens were well tolerated. ABT-450/r/ ombitasvir and dasabuvir without RBV achieves optimal treatment efficacy in HCV genotype 1b-infected patients without cirrhosis

9. Nelson DR, Reddy KR, Di Bisceglie AM, Ferenci P, Crawford DH, Stauber RE, et al. ABT-450/r/ombitasvir + dasabuvir with or without ribavirin in HCV genotype 1-infected patients with history of depression or bipolar disorder: pooled analysis of efficacy and safety in phase 3 trials [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

   Purpose: Interferon (IFN) can exacerbate underlying depression or bipolar disease; thus, many patients with this history are poor candidates for IFN-based therapies. Adults with chronic GT1 hepatitis C virus infection, including those with compensated cirrhosis, achieved SVR12 rates of 90%-100% in phase 3 trials of the interferon-free 3D regimen of ABT-450 (dosed with ritonavir, ABT-450/r), ombitasvir (ABT-267), and dasabuvir (ABT-333) with or without ribavirin (RBV). We evaluated safety and efficacy of 3D+RBV in patients with a history of depression or bipolar disorder (DEP/BPD). Methods: In phase 3 trials, treatment-naive or -experienced cirrhotic and non-cirrhotic patients received at least one dose of 3D+RBV (co-formulated ombitasvir/ABT- 450/r, 25mg/150mg/100mg once daily, dasabuvir 250mg twice daily, + weight-based RBV.) SVR12 rates, incidence of adverse events (AEs) and treatment discontinuation due to AE were determined for patients with and without a history of DEP/BPD at enrollment. Results: A greater percentage of patients with a history of DEP/BPD (357/2052, 17.4%) were female and treatment-experienced versus those without history of DEP/BPD. SVR12 rates were similar for both subgroups (>94.5%); virologic failure occurred in 1 (0.4%) patient with DEP/BPD history. The incidence of any AEs was higher for patients with DEP/BPD history compared to patients without DEP/BPO history; most AEs were mild. The incidence of SAEs (3.6% and 2.4%) and treatment discontinuations due to AEs (1.7% and 0.7%) were comparable among patients with and without DEP/BPD history. Conclusions: In this pooled analysis of phase 3 trial results, high SVR rates and low rates of treatment discontinuation were achieved with the 3D regimen in patients with a history of DEP/BPD. Most AEs were mild. These data support a role for the 3D+RBV regimen among patients who were previously not considered candidates for IFN treatment.

10. Puoti M, Cooper C, Sulkowski MS, Foster GR, Berg T, Villa E, et al. ABT-450/r/ombitasvir + dasabuvir with or without ribavirin in HCV genotype 1-infected patients receiving stable opioid substitution treatment: Pooled analysis of efficacy and safety in phase 2 and phase 3 trials [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

    Purpose: People who inject drugs (PWID) are at the highest risk for chronic hepatitis C virus (HCV)

infection, yet only a minority of PWID initiate treatment and even fewer complete a course of interferon-based therapy. Adults with chronic GT1 hepatitis C virus infection, including those with compensated cirrhosis, achieved high SVR12 rates in phase 2 and 3 trials of the interferon-free 3D regimen of ABT-450 (identified by Abb- Vie and Enanta, dosed with ritonavir, ABT-450/r), ombitasvir, and dasabuvir, with or without ribavirin (RBV). We determined efficacy and safety of the 3D regimen + RBV among HCV GT1-infected patients on chronic opioid substitution treatment (OST) with methadone or buprenorphine in phase 2/3 trials. Methods: Treatment-naive, treatment-experienced, cirrhotic and non-cirrhotic patients included in this analysis were enrolled in phase 3 trials (SAPPHIRE-I or -II, PEARL-II, -III, or -IV, TURQUOISE- II) or phase 2 (AVIATOR, M14-103) trials of 3D+RBV and received at least one dose of study drug at the following or higher dosages: ABT-450 150mg once daily, ritonavir 100mg once daily, ombitasvir 25mg QD, and dasabuvir 250mg twice daily, with or without weight-based RBV. Patients with positive urine tests for illicit substances were excluded. Safety and efficacy were assessed for the subset of patients receiving stable OST. Results: Of 2292 patients in the combined trials, 2.4% (56) were receiving stable OST. The majority were male (66.1%, 37/56) and white (94.6%, 53/56), and the mean age was 47.9 years. Nine patients (16.1%) were treatment-experienced. One patient had compensated cirrhosis. Of the 56 patients, 54 (96.4%) achieved SVR12. A majority of patients (89.3%, 50/56) experienced at least 1 adverse event (AE), most of which were mild. Two patients (3.7%) experienced a serious AE. None of the patients on OST experienced virologic failure; 1 patient (1.8%) discontinued due to an AE at day 26, and 1 patient discontinued for non-compliance. Grade 3 bilirubin elevation occurred in 1 patient (1.8%); there were no grade 3 or greater elevations in ALT, AST, or alkaline phosphatase. Conclusions: In agreement with previous reports, the 3D regimen with or without RBV was well tolerated in patients on stable OST, with a high SVR12 rate of 96.4%, and a favorable toxicity profile. These data suggest that this interferon-free regimen may be a suitable treatment option for this patient population

11. Vierling JM, Puoti M, Bernstein DE, Tsai N, Weiland O, Gomez MR, et al. Efficacy by race or geographic region in HCV genotype 1-infected patients treated with ABT-450/ritonavir/ombitasvir and dasabuvir with or without ribavirin [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

    Purpose: Treatment responses to interferon-containing regimens with a protease inhibitor have historically been lower for black patients compared with white patients. The randomized phase 3 PEARL trials evaluated the safety and efficacy of the "3D" regimen of co-formulated ABT-450/ritonavir/ombitasvir and dasabuvir with or without ribavirin (RBV) in HCV genotype (GT) 1b treatment-experienced (PEARL-II) or treatment-naive (PEARLIII) patients, and in GT1a treatment-naive (PEARL-IV) patients. We assessed treatment response rates based on race or geographic location in a pooled analysis of results from the PEARL trials. Methods: Efficacy by subgroups according to race and geographic region was determined using data from the intentto- treat population of patients enrolled in the PEARL-II (n=179), PEARL-III (n=419), and PEARL-IV (n=305) trials. In each trial, HCV GT1 patients were randomized to 12 weeks of treatment with the 3D regimen plus weight-based RBV, or 3D+RBV placebo (PEARL-III and -IV trials) or 3D without RBV (open-label PEARL-II trial). Results: Of 903 patients in the PEARL trials, 63 were black. In GT1b-infected patients, efficacy with 3D+RBV or 3D treatment was high in all subgroups assessed. In GT1a patients, efficacy with 3D+RBV was high in all subgroups with >10 patients (Table). Among these subgroups, SVR12 rates with 3D treatment in the GT1a subgroups were lower than for 3D+RBV, particularly among black patients and those in North America. Conclusions: In this large international phase 3 program which evaluated the role of RBV, GT1b patients achieved high rates of SVR, regardless of race, geographic region, or addition of RBV. Similar SVR rates were observed in GT1a patients treated with 3D+RBV, while numerically lower SVR rates were observed in GT1a patients treated without RBV, especially in North America and among black patients. (Table Presented)

Other Studies not Meeting the Section Criteria

12. Baran RW, Xie W, Liu Y, Cohen DE, Gooch KL. Health-related quality of life (HRQoL), health state, function and wellbeing of chronic HCV patients treated with interferon-free, oral DAA Regimens: Patient Reported Outcome (PRO) results from the AVIATOR study [abstract]. Hepatology. 2013;58(4 Suppl 1):750A-51A. (Presented at 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013; 2013 Nov 1-5; Washington (DC)).

    Background AVIATOR is a phase 2b trial of multiple interferonfree regimens using 3 DAAs + ribavirin (RBV): ABT-450/r (ritonavir- enhanced protease inhibitor), ABT-267 (NS5A inhibitor), and ABT-333 (non-nucleoside polymerase inhibitor). Overall ITT SVR12 rates after 12-week treatment with 3 DAAs+RBV were 99% in GT1 treatment-naive patients and 93% in prior null responders. PRO results have not previously been reported for oral interferon-free treatment of chronic HCV. Peginterferon plus approved protease inhibitor regimens may impair health state by 15% during treatment [Younossi ZM. DDW 2012]. We report PRO responses in patients receiving 12-week oral DAA treatment regimens in AVIATOR. Methods Three PRO instruments were self-administered at baseline, weeks 4, 8, 12, and post treatment week 24 (PTW24) in AVIATOR: SF-36v.2 HRQoL survey (score 0-100); EQ-5D 5L health state instrument (score 0- 1); and the disease specific HCV-PRO [Baran RW. ILC 2012] function and wellbeing survey (score 0-100). SF-36v.2 Physical Component Score (PCS) and Mental Component Score (MCS) were calculated. Minimum Important Difference (MID) for SF-36 PCS/MCS was defined as 3 points. ITT mean change from baseline is descriptively presented. All patients received 12- week regimens of 3 DAAs+RBV. Results Among 79 treatmentnaive patients/45 null responders, 56%/62% were male, 16%/13% were black, 72%/96% had IL28B non-CC genotype, and mean age was 50.2/49.8 years. PRO completion was > 89% at all assessments. PRO results are summarized in Table 1. Baseline SF-36 PCS/MCS and EQ-5D scores approximated normal population means. Mean PRO scores changed minimally during treatment and no decline in mean SF-36 score reached MID threshold. At PTW 24, all mean scores were improved over baseline. Conclusions Interferon-free DAA regimens in AVIATOR were observed to have minimal impact on PRO response during treatment, suggesting that patient HRQoL, health state, function and wellbeing are preserved. PRO scores at PTW24 were observed to improve compared to baseline. (Table Presented)

13. Eron JJ, Lalezari J, Slim J, Gathe J, Ruane PJ, Wang C, et al. Safety and efficacy of ombitasvir - 450/r and dasabuvir and ribavirin in HCV/HIV-1 co-infected patients receiving atazanavir or raltegravir ART regimens. J Int AIDS Soc. 2014;17(4 Suppl 3):19500, 2014. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4224905

    OBJECTIVE: Whether concomitant HIV antiretroviral therapy (ART) affects the safety and efficacy of interferon-free HCV therapies or whether HCV treatment may negatively affect HIV control is unclear. We assessed the 3 direct-acting antiviral (3D) regimen of ombitasvir, ABT-450 (identified by AbbVie and Enanta; co-dosed with ritonavir) and dasabuvir with ribavirin (RBV) in HCV/HIV-1 co-infected patients with and without cirrhosis, including HCV treatment-experienced, receiving atazanavir (ATV)- or raltegravir (RAL)-based ART therapy
    METHODS: HCV genotype 1-positive treatment-naive or pegIFN/RBV-experienced patients, with or without Child-Pugh A cirrhosis, CD4+ count >200 cells/mm(3) or CD4 + % >14%, and plasma HIV-1 RNA suppressed on stable ART received open-label 3D + RBV for 12 or 24 weeks. Rates of HCV-sustained virologic response at post-treatment weeks 4 and 12 (SVR4 and SVR12, respectively) and bilirubin-related adverse events (AEs) are reported from post-hoc analyses for subgroups defined by treatment duration and ART regimen
    RESULTS: The SVR12 rate for patients receiving 12 weeks of 3D + RBV was 93.5% with comparable rates in patients receiving either ATV (93.8%) or RAL therapy (93.3%) (Table 1). The SVR4 rate for the 24-week arm was 96.9% with a single virologic breakthrough at treatment week 16 in a patient receiving RAL therapy. Patients receiving concomitant ATV had more AEs related to indirect hyperbilirubinemia including ocular icterus, jaundice and grade 3 or 4 elevations in total

bilirubin (predominantly indirect). No patient discontinued the study due to AEs, and no serious AEs were reported during or after treatment. No patient had a confirmed plasma HIV-1 RNA value >200 copies/mL during the treatment period
CONCLUSIONS: In this first study to evaluate an IFN-free regimen in HCV genotype 1-positive treatment-naive and experienced patients with HIV-1 co-infection, including those with cirrhosis, high rates of SVR were comparable to those with HCV monoinfection. Indirect hyperbilirubinemia was consistent with the known ABT-450 inhibition of the OATP1B1 bilirubin transporter, RBV-related haemolytic anaemia and inhibitory effect of ATV on bilirubin conjugation. The laboratory abnormalities and AEs observed did not negatively affect treatment response or lead to treatment discontinuation

14. Fried MW, Forns X, Reau N, Wedemeyer H, Shiffman ML, Castro A, et al. Turquoise-II: Regimens of ABT-450/r/ombitasvir and dasabuvir with ribavirin achieve high SVR12 rates in HCV genotype 1-infected patients with cirrhosis, regardless of baseline characteristics [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

    Purpose: Efficacy of interferon-containing therapies in HCV-infected patients (pts) are affected by factors including more advanced liver disease, as may be clinically evidenced by hypoalbuminemia or thrombocytopenia. ABT-450 is an HCV NS3/4A protease inhibitor (dosed with ritonavir, ABT-450/r) identified by AbbVie and Enanta. Ombitasvir (ABT-333) is an NS5A inhibitor; dasabuvir (ABT-267) is an NS5B RNA polymerase inhibitor. The phase 3 TURQUOISE-II trial examined efficacy and safety of an all-oral regimen of co-formulated ABT-450/r/ombitasvir+dasabuvir with ribavirin (3D+RBV) in treatment (tx)-naive and tx-experienced pts with HCV genotype (GT) 1 infection and compensated (Child-Pugh A) cirrhosis. We report efficacy by baseline pt and disease characteristics. Methods: In this open-label trial, pts were randomized to receive 3D+RBV for 12 or 24 weeks. SVR12 rates were calculated for all pts and for pt subgroups. SVR12 rates are reported for select subgroups; rates for additional subgroups will be presented. Results: 380 pts were randomized and received study drug. Overall SVR12 rates were 91.8% and 95.9% for the 12-and 24-week arms, respectively. SVR12 rates did not differ substantially by sex, age, body-mass index, or HCV RNA (Figure). SVR12 rates were 88.9-97.0% in pts with platelet counts <100x109/L and 84.0-88.9% in pts with serum albumin <35g/L. Conclusions: Among pts with HCV GT1 infection and cirrhosis, SVR12 rates with 3D+RBV were high across a broad range of subgroups, including pts with evidence of impaired hepatic synthetic function and/or evidence of portal hypertension. (Figure presented)

15. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R, et al. An Interferon-free Antiviral Regimen for HCV after Liver Transplantation. N Engl J Med. 2014 Nov 11.

    Background Hepatitis C virus (HCV) infection is the leading indication for liver transplantation worldwide, and interferon-containing regimens are associated with low response rates owing to treatment-limiting toxic effects in immunosuppressed liver-transplant recipients. We evaluated the interferon-free regimen of the NS5A inhibitor ombitasvir coformulated with the ritonavir-boosted protease inhibitor ABT-450 (ABT-450/r), the nonnucleoside NS5B polymerase inhibitor dasabuvir, and ribavirin in liver-transplant recipients with recurrent HCV genotype 1 infection. Methods We enrolled 34 liver-transplant recipients with no fibrosis or mild fibrosis, who received ombitasvir-ABT-450/r (at a once-daily dose of 25 mg of ombitasvir, 150 mg of ABT-450, and 100 mg of ritonavir), dasabuvir (250 mg twice daily), and ribavirin for 24 weeks. Selection of the initial ribavirin dose and subsequent dose modifications for anemia were at the investigator's discretion. The primary efficacy end point was a sustained virologic response 12 weeks after the end of treatment. Results Of the 34 study participants, 33 had a sustained virologic response at post-treatment weeks 12 and 24, for a rate of 97% (95% confidence interval, 85 to 100). The most common adverse events were fatigue, headache, and cough. Five patients (15%) required erythropoietin; no patient required blood transfusion. One patient discontinued the study drugs owing to adverse events after week 18 but had a sustained virologic response. Blood levels of calcineurin inhibitors were monitored, and dosages were modified to maintain therapeutic levels; no episode of graft rejection was observed during the

study. Conclusions Treatment with the multitargeted regimen of ombitasvir-ABT-450/r and dasabuvir with ribavirin was associated with a low rate of serious adverse events and a high rate of sustained virologic response among liver-transplant recipients with recurrent HCV genotype 1 infection, a historically difficult-to-treat population. (Funded by AbbVie; CORAL-I ClinicalTrials.gov number, NCT01782495)

16. Wedemeyer H, Forns X, Craxi A, Reau N, Kwo P, Bourgeois S, et al. Safety comparison of 12- and 24-week treatments in HCV genotype 1-infected patients with cirrhosis: Results from TURQUOISE-II [abstract]. J Gastroenterol Hepatol. 2014;29(Suppl 2):155. (Presented at Australian Gastroenterology Week 2014 Broadbeach; 2014 Oct 22-24; QLD Australia).

    Objective: Interferon-containing protease inhibitor regimens have been associated with a high rate of serious adverse events (AEs) in patients with cirrhosis.1We report the safety of the 3 direct-acting antiviral (3D) regimen of ABT-450 (identified by AbbVie and Enanta) co-dosed with ritonavir (r), ombitasvir (formerly ABT-267) and dasabuvir (formerly ABT-333) with ribavirin (RBV) in the treatment of 380 HCV genotype 1-infected patients with cirrhosis. Methods: Patients were randomized to receive the 3D+RBV regimen for 12 (N = 208) or 24 weeks (N = 172). Key eligibility criteria included: Child-Pugh A cirrhosis, platelet count >60,000 cells/mm3, serum albumin >2.8 g/dL, and total bilirubin <3 mg/dL. Treatment-emergent AEs from the time of study drug administration until 30 days after last dose for all patients who received >1 dose of study drug are reported. Results: The percentage of patients experiencing any AE, severe, or serious AEs were similar in both arms. AEs were mostly mild or moderate in severity. The most common AEs in the 12- and 24-week arms respectively, were fatigue (32.7% vs. 46.5%), headache (27.9% vs. 30.8%), and nausea (17.8% vs. 20.3%). Four (1.1%) patients experienced AEs consistent with hepatic decompensation but were considered unrelated to study drugs. Five of 380 (1.3%) patients experienced serious AEs that were assessed by the investigator to have reasonable possibility of being related to the 3D regimen. All patients who modified RBV dose for any reason, 4 patients who received erythropoietin, and 2 patients who received a transfusion all achieved SVR12. Conclusions: The 3D+RBV regimens were generally well tolerated, with no clinically significant differences in safety profiles based on treatment duration. AEs reported in this study of 380 patients with cirrhosis were generally consistent with those demonstrated for the 3D+RBV regimen in previous studies of patients without cirrhosis

17. Wyles DL, Sulkowski MS, Eron JJ, Trinh R, Lalezari J, Slim J, et al. Turquoise-i: 94% Svr12 in hcv/hiv-1 coinfected patients treated with abt-450/r/ombitasvir, dasabuvir and ribavirin [abstract]. Abstract presented at: Hepatology Conference: 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2014; 2014 Nov 8-10; Boston (MA).

    Objective: Interferon based treatment options for HCV/HIV-1 coinfected patients (pts) have sub-optimal efficacy and limited studies have been conducted evaluating interferon-free HCV treatment regimens in this population. The 3 direct-acting antiviral (3D) regimen of ABT-450 (identified by AbbVie and Enanta; co-dosed with ritonavir), ombitasvir, and dasabuvir with ribavirin (RBV) achieves high sustained virologic response (SVR) rates in HCV genotype (GT) 1-monoinfected pts. The 3D+RBV regimen was assessed in adults with HCV GT1/HIV-1 coinfection with and without cirrhosis. Methods: TURQUOISE-I is a randomized, open-label study evaluating the 3D+RBV regimen for 12 or 24 weeks. HCV treatment-naive or pegIFN/RBV-experienced pts, with or without Child-Pugh A cirrhosis, CD4+ count >200 cells/mm3 or CD4+ % >14%, and plasma HIV-1 RNA suppressed on a stable atazanavir- or raltegravir-inclusive antiretroviral (ART) regimen were included. The primary endpoint is sustained virologic response weeks post-treatment (SVR12). Results: Among pts treated with 3D+RBV for 12 weeks, 29/31 (93.5%) achieved SVR12. One pt withdrew consent prior to finishing treatment but had an undetectable HCV RNA at last study visit (week 10). Another pt experienced relapse at post-treatment week 2. Among pts receiving 24 weeks of treatment, 31/32 (96.9%) achieved EOTR; 1 pt experienced on-treatment HCV breakthrough at week 16. Adverse events (AEs) were generally mild, and no serious AE or discontinuations due to an AE were reported. The most common AEs were fatigue, insomnia, and nausea. Elevation in total bilirubin was the most common laboratory abnormality, occurring predominantly in pts receiving atazanavir. To

date, 1 pt in each arm has had a confirmed HIV-1 RNA >40 copies/ mL (but <200 copies/mL) that re-suppressed while maintaining the same HIV-1 ART regimen without 3D+RBV interruption. Conclusions: In treatment-naive and -experienced GT1 HCV/ HIV-1 coinfected pts with or without cirrhosis, the high rates of virologic response and low rate of treatment discontinuation were consistent with those in HCV GT1-monoinfected populations receiving 3D+RBV. (Table Presented)

Harvoni:

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