

# Interferon-free antiviral combination therapies without nucleosidic polymerase inhibitors

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## Summary

The establishment of robust HCV cell culture systems and characterization of the viral life cycle provided the molecular basis for highly innovative, successful years in HCV drug development. With the identification of direct-acting antiviral agents (DAAs), such as NS3/4A protease inhibitors, NS5A replication complex inhibitors, nucleotide and non-nucleoside polymerase inhibitors, as well as host cell targeting agents, novel therapeutic strategies were established and competitively entered clinical testing. The first-in-class NS3/4A protease inhibitors telaprevir and boceprevir, approved in 2011, were recently outpaced by the pan-genotypic nucleotide polymerase inhibitor sofosbuvir that in combination with pegylated interferon and ribavirin, further shortens therapy durations and also offers the first interferon-free HCV treatment option. In the challenging race towards the goal of interferon-free HCV therapies, however, several oral DAA regimens without nucleotide polymerase inhibitors that combine a NS3/4A protease inhibitor, a NS5A inhibitor and/or a non-nucleoside polymerase inhibitor yielded competitive results. Second generation NS3/4A protease and NS5A inhibitors promise an improved genotypic coverage and a high resistance barrier. Results of novel DAA combination therapies without the backbone of a nucleotide polymerase inhibitor, as well as treatment strategies involving host targeting agents are reviewed herein.

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## Introduction

Hepatitis C virus (HCV) infection is a major public health burden with an estimated 185 million anti-HCV positive individuals worldwide [1]. The risk for the development of HCV-related complications such as liver cirrhosis and the rising incidence of HCV-related hepatocellular carcinoma have encouraged the development of novel, effective therapeutic strategies [2]. Particularly, unravelling of the HCV life cycle, enabled by the availability of robust HCV cell culture systems, afforded the opportunity to identify direct-acting antiviral drug targets and respective antiviral agents [3–5]. In fact, numerous direct-acting antiviral agents (DAAs) belonging to different drug classes, such as NS3/4A protease inhibitors, NS5A replication complex inhibitors, nucleos(t)ide and non-nucleoside polymerase inhibitors have been developed (reviewed in [6]; Table 1A). Also, host-targeting agents (HTAs) that act against cellular pathways involved in viral entry or replication, could be identified [7] (Table 1B). So far, clinical trials investigating the different drug classes and their combinations with or without pegylated interferon (PegIFN) and/or ribavirin (RBV) yielded highly promising sustained virologic response (SVR) rates [6]. The proof that successful clearance of HCV is possible with an all-oral DAA combination further stimulated clinical trials, investigating novel, interferon-free DAA combination therapies [8]. About two years after the NS3/4A protease inhibitors telaprevir and boceprevir, used in combination with PegIFN and RBV, became available, the first nucleotide polymerase inhibitor sofosbuvir was approved [9–11]. Sofosbuvir offers the first interferon-free therapeutic option (particularly for HCV genotypes 2 and 3) and, in combination with PegIFN and RBV, further shortens the therapy duration in HCV genotype 1 (and 3, 4, 5, 6) infected patients [12–14].

Nucleotide polymerase inhibitors have a high barrier to resistance and confer a potent, pan-genotypic activity. Combination of sofosbuvir with other DAAs, such as NS3/4A protease inhibitors and NS5A inhibitors further improves SVR rates even in difficult to cure patient populations [15–20].

Interferon-free regimens without the backbone of a nucleosidic polymerase inhibitor depend on combinations of two or more DAAs with or without RBV, which is explained by a low barrier to resistance of first generation NS3/4A protease-, NS5A-, and non-nucleoside polymerase inhibitors. First generation NS3/4A protease inhibitors and non-nucleoside polymerase inhibitors have limited genotypic coverage (predominantly HCV genotype 1).

**Keywords:** Direct-acting antiviral agents (DAAs); All oral; Interferon-free HCV treatment; NS3/4A protease inhibitors (PI); NS5A inhibitors; Non-nucleoside polymerase inhibitors (NNI); Host-targeting agents (HTAs).

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**Abbreviations:** HCV, hepatitis C virus; DAA(s), direct-acting antiviral agent(s); PI, NS3/4A protease inhibitor; NI, nucleos(t)ide analogue polymerase inhibitor; NNI, non-nucleoside polymerase inhibitor; HTA(s), host-targeting agent(s); QD, one daily; BID, twice daily; TID, thrice daily; RAV(s), resistance associated variant(s); PegIFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.



Second generation NS3/4A protease inhibitors such as MK-5172, ABT-493, promise an improved genotypic coverage and a higher resistance barrier [21,22]. First and second generation NS5A inhibitors differ less in their genotypic coverage, but the barrier to resistance seems to be enhanced in second generation compounds (i.e., MK-8742, GS-5816, GSK2336805, ABT-530) [23–26].

This review provides an overview over recent IFN-free DAA combination trials without nucleoside/nucleotide analogue polymerase inhibitors.

**Key Points**

- DAA combination trials, particularly those involving the combination of a NS3/4A protease inhibitor and a NS5A inhibitor, or triple DAA combination therapies, additionally including a non-nucleoside polymerase inhibitor, report excellent virologic response rates in HCV genotype 1 therapy naïve and experienced patients, including patients with liver cirrhosis
- Ongoing efforts in HCV drug development include the investigation of second generation NS3/4A protease inhibitors and NS5A replication complex inhibitors that promise an improved genotypic coverage and higher resistance barrier
- The future role of host targeting agents needs to be defined

**Interferon-free, all-oral DAA combination trials without nucleotide polymerase inhibitors**

*Combination of a NS3/4A protease inhibitor, a NS5A inhibitor ± RBV*

All-oral, interferon-free DAA trials, investigating the combination of a NS3/4A protease inhibitor and a NS5A inhibitor (with or without RBV), yielded favourable results (summarized in Table 2).

*ABT-450/r and ombitasvir (ABT-267) ± RBV*

Combination of the ritonavir-boosted NS3/4A protease inhibitor ABT-450/r and the NS5A inhibitor ombitasvir (formerly ABT-267) was first investigated in the AVIATOR study [27]. This phase 2b open-label trial enrolled non-cirrhotic HCV genotype (GT) 1-infected patients who were either treatment-naïve or null-responders to prior therapy with PegIFN and RBV. Patients were randomly assigned to one of fourteen treatment arms where they received different doses of ABT450/r (100/100 mg, 150/100 mg, or 200/100 mg QD), in combination with ombitasvir (25 mg QD) or the non-nucleoside polymerase inhibitor dasabuvir (formerly ABT-333, 400 mg BID), with or without RBV. Therapy durations were 8, 12 or 24 weeks. SVR rates in treatment-naïve patients (n = 79) and prior null-responders (n = 45) who received ABT-450/r, ombitasvir, and RBV for 12 weeks were 89% for both groups. Results for other treatment arms (combinations of ABT450/r, dasabuvir and RBV, or triple DAA combinations) are reviewed below.

Substudy 1 of the phase 2 PEARL-I trial investigated the efficacy of ABT450/r and ombitasvir (ABT-267), with or without RBV, for 12 weeks in non-cirrhotic, treatment-naïve or experienced patients with HCV GT1b or GT4 infection [28,29]. SVR12 rates were 95.2% and 90.0% in HCV GT1b-infected treatment-

naïve (n = 42) and prior null-responders (n = 40), respectively, treated with a RBV-free combination of ABT-450/r (150/100 mg QD) and ombitasvir (25 mg QD) for 12 weeks [28]. Also, all of the 42 treatment-naïve HCV GT4-infected patients randomized to the RBV-containing DAA regimen and 90.9% of the patients treated with ABT-450/r and ombitasvir alone (n = 44) had a SVR [29]. SVR12 results for treatment-experienced HCV GT4 patients (n = 49) are not yet available.

Substudy 2 of the PEARL-1 trial investigates the efficacy of ABT-450/r and ombitasvir for 24 weeks in therapy naïve and experienced HCV GT1b patients with liver cirrhosis. Results are not yet available.

An ongoing open-label, phase 2 pilot study investigates the combination of ABT-450/r and the next-generation NS5A inhibitor ABT-530, with and without RBV for 12 weeks in therapy naïve, HCV GT3-infected patients without cirrhosis [30].

*Sovaprevir and ACH-3102 + RBV*

The all-oral combination of sovalprevir, a next-generation NS3/4A protease inhibitor (200 mg or 400 mg QD, n = 10 patients in each group) and ACH-3102 (150/50 mg), a second generation NS5A inhibitor and RBV was investigated in a placebo controlled, open-label phase 2 study [31]. 100% of HCV GT1b patients (n = 4 in each verum arm) achieved a SVR12. Suboptimal SVR rates, however, were reported for HCV GT1a-infected patients who experienced viral breakthrough (after week 2) or relapse. In all of the treatment failures, NS3/4A resistance mutations were detected at position 155. Also, most of the GT1a patients had 2 or more resistance associated variants in the NS5A protein. Sovaprevir was placed on clinical hold after liver enzyme elevation was reported from a phase 1 drug-drug interaction study, but clinical development was recently resumed [32].

*Asunaprevir and daclatasvir*

A small exploratory phase 2a study investigated the interferon-free all oral combination of the NS3/4A protease inhibitor asunaprevir (ASV, 600 mg BID) and the first-in class, once-daily NS5A inhibitor daclatasvir (DCV, 60 mg QD) for 24 weeks in eleven HCV genotype 1 null-responders to previous therapy with PegIFN and RBV [8]. A sustained virologic response was achieved in 2/2 HCV genotype 1b-infected patients but in only 2/9 (22.2%) HCV genotype 1a-infected patients, due to high breakthrough rates.

The efficacy of this dual, RBV-free DAA regimen was further investigated in several phase 2 studies, conducted in Japan and the U.S. (summarized in Table 3) [33,34]. In the U.S. study (NCT01012895), SVR24 rates in non-cirrhotic HCV genotype 1b null-responders treated with asunaprevir 200 mg BID (group A1, n = 18) or asunaprevir 200 mg QD and daclatasvir (60 mg QD) (group A2, n = 20) for 24 weeks were 83% and 60% respectively [34]. Most of the HCV GT1a-infected patients, treated with asunaprevir 200 mg BID and daclatasvir 60 mg QD and RBV (group B3, n = 22), experienced viral breakthrough.

Results of the asunaprevir/daclatasvir phase 3 program that investigated the 24 week dual combination of asunaprevir (100 mg BID) and daclatasvir (60 mg QD), restricted to HCV genotype 1b-infected patients with and without cirrhosis, were reported recently [35,36]. In the Japanese phase 3 trial, SVR rates were 87.4% in interferon ineligible/intolerant patients (n = 135)

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**Table 1. Overview over selected direct-acting antiviral agents (DAAs) and selected host-targeting agents for HCV therapy.** (A) Overview over selected direct-acting antiviral agents (DAAs), not including nucleos(t)ide analogues. (B) Overview over selected host-targeting agents for HCV therapy.

## A

Direct-acting antiviral agents (DAAs)	Company	Clinical development
<b>NS3/4A protease inhibitors</b>		
<i>Linear</i>		
<b>Boceprevir (BOC)</b>	<b>Merck</b>	<b>Approved</b>
<b>Telaprevir (TPV)</b>	<b>Vertex/Janssen</b>	<b>Approved</b>
ABT-450/r*	AbbVie	Phase 3
ABT-493	AbbVie	Phase 2
Faldaprevir (BI 201335)	Boehringer-Ingelheim	Discontinued after completion of phase 3
Asunaprevir (ASV, BMS-650032)	Bristol-Myers Squibb	Phase 3
Vedoprevir (GS-9451)	Gilead	Phase 2
Narlaprevir (SCH 900518)	Merck	Phase 2
Vaniprevir (MK-7009)	Merck	Phase 3
Sovaprevir (ACH-1625)	Achillion	Phase 2
<i>Macrocyclic</i>		
<b>Simeprevir (TMC435)</b>	<b>Janssen</b>	<b>Approved</b>
MK-5172	Merck	Phase 3
Danoprevir (DNL/r, RG-7227)*	Roche	Phase 3
ACH-2684	Achillion	Phase 2
GS-9256	Gilead	Discontinued
BZF-961	Novartis	Phase 1
<b>NS5A inhibitors</b>		
<b>Daclatasvir (DCV, BMS-790052)</b>	<b>Bristol-Myers-Squibb</b>	<b>Approved</b>
Ombitasvir (ABT-267)	AbbVie	Phase 3
ABT-530	AbbVie	Phase 2
ACH-3102	Achillion	Phase 2
Ledipasvir (LDV, GS-5885)**	Gilead	Phase 3
GS-5816**	Gilead	Phase 2
GSK2336805	GlaxoSmithKline	Phase 2
Samatasvir (IDX719)	Idenix Pharmaceuticals	Phase 2
MK-8742	Merck	Phase 3
EDP239	Novartis	Phase 1
PPI-461	Presidio	Phase 1
PPI-668	Presidio	Phase 2
<b>Non-nucleoside polymerase inhibitors</b>		
<i>Thumb I</i>		
Deleobuvir (BI 207127)	Boehringer-Ingelheim	Discontinued after completion of phase 3
BMS-791325	Bristol-Myers-Squibb	Phase 3
TMC647055	Medivir/Janssen	Phase 2
<i>Thumb II</i>		
GS-9669	Gilead	Phase 2
Lomibuvir (VX-222 )	Vertex	Phase 2
<i>Palm I</i>		
ABT-072	AbbVie	Discontinued
Dasabuvir (ABT-333)	AbbVie	Phase 3
Setrobuvir (ANA-598, RO5466731)	Roche	Discontinued
<i>Palm II</i>		
Tegobuvir (GS-9190)	Gilead	Discontinued

(Continued on next page)

Table 1 (continued).

**B**

Host targeting agent (HTAs)	Company	Clinical development
<b>Cyclophilin A inhibitors</b>		
Alisporivir	Novartis	Phase 2
SCY-635	Scynexis	Phase 2
<b>MicroRNA-122</b>		
Miravirsen	Santaris	Phase 2

<sup>\*/r</sup>, Ritonavir-boosted.

<sup>\*\*</sup>, Fixed-dose combinations of sofosbuvir/ledipasvir and sofosbuvir/GS-5816.

and 80.5% in prior non-responders (null, partial, n = 87) to therapy with PegIFN and RBV [35]. SVR rates of the placebo-controlled “HALLMARK-DUAL” were reported with 90% in treatment-naïve, 82% in ineligible/intolerant patients, and 82% in non-responder patients [36]. In both trials, treatment responses were independent of the *IL28B* genotype (*IL28B*-CC vs. non-CC), and prior treatment experience. Also, response rates were similar in non-cirrhotic and cirrhotic patients (90.9% vs. 84% in the Japanese study and 84% and 85% in the “HALLMARK-DUAL” study). Overall, the dual DAA combination was well tolerated with a manageable adverse event (AE) profile and low number of treatment discontinuations. Common adverse events included fatigue, nausea, diarrhoea, headache and asthenia.

*Simeprevir and daclatasvir ± RBV*

The LEAQUE-1 study, a randomized, open-label, phase 2 study investigated the oral combination of the NS3/4A protease inhibitor simeprevir (150 mg QD) and a lower dose of daclatasvir (30 mg) in HCV genotype 1b-infected, treatment-naïve patients (n = 104) or patients with prior null response to PegIFN and RBV (n = 43), including patients with cirrhosis [37]. Patients were randomized to treatment with DCV/SMV either with or without RBV for 12 weeks. At week 12, patients were re-randomized to stop treatment or to continue therapy for another 12 weeks. A small cohort of HCV genotype 1a-infected patients (n = 12 therapy naïve and n = 9 null-responder to previous PegIFN and RBV) were treated with both DAAs plus RBV for 24 weeks. Response rates were 75–85% and 65–95% in HCV GT1b treatment-naïve and prior null-responders with HCV genotype 1 infection, respectively. For HCV GT1a-infected treatment-naïve patients, SVR12 rates were reported with 67%. GT1a null-responders were offered rescue therapy with addition of PegIFN after five patients experienced viral breakthrough.

The 24-week combination of simeprevir (150 mg) and a higher dose of daclatasvir (60 mg), and RBV is currently investigated in HCV GT1b-infected patients with recurrent HCV infection after orthotopic liver transplantation, results are not yet available [38].

*Simeprevir and samatasvir + RBV*

The HELIX-1 study investigated the oral combination of simeprevir (150 mg) and samatasvir (25, 50, 100, and 150 mg), a second

generation NS5A inhibitor, in treatment-naïve, non-cirrhotic HCV genotype 1b- or 4-infected patients [39]. SVR4 rates were 47–80% for HCV GT1b patients (n = 84) and 100% for HCV GT4 patients (n = 9).

*Combination of the second generation NS3/4A inhibitor MK-5172 and MK-8742 ± RBV*

Recently, results were also presented from the phase 2 C-WORTHY trial [40–42]. This study, a two-part, parallel-group, randomized (within group) clinical trial, investigated the all-oral, interferon-free, once daily, fixed dose combination of the second generation NS3/4A protease inhibitor MK-5172 and MK-8742, a NS5A replication complex inhibitor. Overall, the study included 471 HCV genotype 1 patients that were enrolled across 16 arms. C-WORTHY, part A, included 65 HCV treatment-naïve genotype 1 patients without cirrhosis who received MK-5172 (100 mg QD) and MK-8742 (20 or 50 mg QD), with or without RBV for 12 weeks. All HCV GT1a-infected patients were randomized to RBV containing arms. SVR12 rates, as reported at AASLD 2013, were 89–100%. In HCV genotype 1b patients the presence or absence of RBV did not impact SVR rates [40].

Treatment with MK-5172/MK-8742 (50 mg QD) ± RBV was expanded to several groups. These included (1) treatment-naïve, non-cirrhotic patients (C-WORTHY, part B), investigating the dual DAA combination with or without RBV for 8 or 12 weeks; (2) treatment-naïve cirrhotic patients (n = 123); and (3) non-cirrhotic and cirrhotic null-responders to previous therapy with PegIFN and RBV (n = 130). Groups (2) and (3) received 12 or 18 weeks of MK-5172/MK-8742 either with or without RBV.

Results of the combined analysis of C-WORTHY part A and part B were presented at EASL 2014. SVR8 rates, available for 93% of the patients who received MK-5172/MK-8742 and RBV for 8 weeks, were 83%. SVR24 results were available for 100% of the patients who were enrolled into part A, SVR8 data for 93% of the part B participants. Combined response rates were 94% and 98% for a twelve week treatment with MK-5172/MK-8742 with and without RBV, respectively. Also, SVR4/8 rates were reported with 90–97% and 91–100% for (1) and (2), respectively [41,42].

The oral combination of MK-5172 and MK-8742 was generally safe and well tolerated. Common AEs (≥10%) reported in different study arms comprised fatigue, headache, nausea, diarrhoea, asthenia, and insomnia. Anaemia was not reported in the RBV

Table 2. Summary of selected clinical trials investigating the combination of a NS3/4A protease inhibitor and a NSSA inhibitor ± RBV.

Sponsor	Trial name or NCT ID	Phase	DAA combination	RBV	Patient population	Treatment (wk)	Outcome (SVR)
AbbVie	<b>AVIATOR</b>	2	ABT-450/r + ombitasvir	+ RBV	HCV GT1, therapy naïve and experienced (prior null-responders), no cirrhosis	12	Naïve: 89% Null-responders: 89%
	<b>PEARL-I</b>	2	ABT-450/r + ombitasvir	∅ RBV	HCV GT1b, naïve, prior null-responders, no cirrhosis	12	Naïve: 95.2 %, null-responders: 90% Naïve: 100% (+RBV), 91% (∅ RBV) Experienced: SVR12 not yet available
				± RBV	HCV GT4, naïve, experienced (prior partial-/null-responder, relapser), no cirrhosis	12	
				<b>Substudy 2</b> HCV GT1b, naïve, experienced, cirrhosis		24	
	<b>NCT02068222</b>	2	ABT-450/r + ABT-530	± RBV	HCV GT3, naïve, no cirrhosis	12	Ongoing
Achillion	<b>NCT01849562</b>	2	Sovaprevir + ACH-3102	+ RBV	HCV GT1, naïve, no cirrhosis	12	Naïve, GT1b 100%
Bristol-Myers-Squibb	<b>NCT01012895</b>	2	Asunaprevir + daclatasvir	∅ RBV	HCV GT1, prior null-responders, no cirrhosis	24	GT1a: 22% GT1b: 100%
	<b>NCT01051414</b>	2	Asunaprevir + daclatasvir (Japan)	∅ RBV	HCV GT1b, prior null responder; PegIFN intolerant/ineligible, no cirrhosis	24	Null-responders: 90.5% Ineligible/intolerant: 63.6%
	<b>NCT01012895</b>	2	Asunaprevir + daclatasvir (US)	± RBV	HCV GT1, prior null-responder, no cirrhosis	24	60-83% (GT1b)
	<b>NCT01497834</b>	3	Asunaprevir + daclatasvir (Japan)	∅ RBV	HCV GT1b, PegIFN intolerant/ineligible, prior null-/partial responder ± cirrhosis	24	Ineligible/intolerant: 87.4% Null/partial responder 80.5%
	<b>Hallmark-Dual</b>	3	Asunaprevir + daclatasvir	∅ RBV	HCV GT1b, naïve, PegIFN intolerant/ineligible, prior null-/partial responder, ± cirrhosis	24	Naïve: 90% Ineligible/intolerant: 82% Null/partial responder: 82%
Bristol-Myers-Squibb/Janssen	<b>LEAQUE-1</b>	2	Simeprevir + daclatasvir	± RBV	HCV GT1, naïve, prior null-responder, no cirrhosis	12, 24	Naïve, GT1b: 75-85% Null-responder, GT1b: 65-95% Naïve, GT1a: 67%
	<b>NCT01938625</b>	2	Simeprevir + daclatasvir	+ RBV	HCV GT1b, recurrent chronic HCV infection after orthotopic liver transplantation	24	Ongoing
Janssen/Merck	<b>HELIX-1</b>	1,4	Simeprevir + samatasvir	+ RBV	HCV GT1b, 4, naïve, no cirrhosis	12	GT1b 47-80% GT4: 100%
Merck	<b>C-WORTHY</b>	2	MK-5172/MK-8742	± RBV	HCV GT1, naïve, no cirrhosis (Part A) expansion cohorts: naïve, ± cirrhosis; null responders ± cirrhosis	12	Naïve, no cirrhosis: 89-100% (Part A) Expansion groups ongoing
				± RBV		8, 12; 12, 18	
	<b>C-SCAPE</b>	2	MK-5172/MK-8742	± RBV	HCV GT2, 4-6, treatment-naïve, no cirrhosis	12	Ongoing
	<b>C-SALVAGE</b>	2	MK-5172/MK-8742	+ RBV	HCV GT1 treatment-experienced (incl. DAA failure) ± cirrhosis	12	Ongoing
	<b>C-EDGE TN</b>	3	MK-5172 + MK-8742	∅ RBV	HCV GT1, 4-6, naïve, ± cirrhosis	12	Ongoing
	<b>C-EDGE TE</b>	3	MK-5172 + MK-8742	± RBV	HCV GT1, 4-6, experienced (incl. DAA failure) ± cirrhosis	12, 16	Ongoing
	<b>NCT02115321</b>	2/3	MK-5172 + MK-8742	∅ RBV	HCV GT1, 4-6, naïve, CHILD B cirrhosis	12	Ongoing
<b>NCT01932762</b>	2	MK-5172 + MK-8742	± RBV	GT 2, 4, 5, and 6, naïve, no cirrhosis	12	Ongoing	

**Table 3. Summary of selected clinical trials investigating the combination of a NS3/4A protease inhibitor and a non-nucleoside polymerase inhibitor ± RBV.**

Sponsor	Trial name or NCT ID	Phase	DAA combination	RBV	Patient population	Treatment (wk)	Outcome (SVR)
AbbVie	<b>AVIATOR</b>	2	ABT-450/r + dasabuvir	+ RBV	HCV GT1, naïve, no cirrhosis	12	Naïve: 83%
	<b>CO-PILOT</b>	2	ABT-450/r + dasabuvir	+ RBV	HCV GT1, naïve, prior null or partial responder, no cirrhosis	12	Naïve: 79-89% Experienced: 47%
	<b>PILOT</b>	2	ABT-450/r + ABT-072	+ RBV	HCV GT1, <i>IL28B</i> CC, naïve, no cirrhosis	12	Naïve: 91%

free-arms. The numbers of discontinuations, due to laboratory abnormalities, AEs and SAEs were generally low ( $\leq 3\%$  in study arms that included patients with cirrhosis, respectively).

The results of additional phase 2 trials, involving the combination MK-5172/MK-8742 ± RBV, are pending, the phase 3 study program has just started (Table 2).

Ongoing or planned trial activities also include assessment of this DAA combination in patients with Child-Pugh-B cirrhosis and HCV GT2- and 3-infected patients [43,44].

*Combination of a NS3/4A protease inhibitor, a non-nucleoside polymerase inhibitor ± RBV*

Several trials investigated the combination of a NS3/4A protease inhibitor, a non-nucleoside polymerase inhibitor with or without RBV (Table 3).

*ABT-450/r and dasabuvir (ABT-333) + RBV*

The combination of the NS3/4A protease inhibitor ABT-450/r, the non-nucleoside polymerase inhibitor dasabuvir and RBV was investigated in the phase 2 AVIATOR and CO-PILOT study [27,45]. In the AVIATOR study (outlined above) response rates for 41 treatment-naïve patients without cirrhosis treated with ABT-450/r (150/100 mg QD), dasabuvir (400 mg BID) and RBV for 12 weeks were 83% [27]. The CO-PILOT study tested ABT450/r (250 mg/100 mg or 150 mg/100 mg) in combination with dasabuvir (400 mg BID) and RBV for 12 weeks in non-cirrhotic treatment-naïve HCV genotype 1 patients (group 1: n = 19 and group 2: n = 14 patients) and patients with prior partial or null response to PegIFN and RBV (group 3: n = 17) [45]. Reported SVR rates were 89%, 79%, and 47% in groups 1, 2, and 3, respectively.

*ABT-450/r and ABT-072 + RBV*

The PILOT study investigated a 12 week oral combination treatment of ABT-450/r (150/100 mg QD) and the non-nucleoside polymerase inhibitor ABT-072 (400 mg QD) and RBV in 11 treatment-naïve, non-cirrhotic HCV genotype 1 patients with the *IL28B*-CC genotype [46]. 10 patients (91%) had a SVR24. One patient relapsed 36 weeks after the end of treatment. At the time of relapse, a NS5B resistance variant (Y448H), that was not present in the baseline sample, was detected. Clinical development of ABT-072 is currently not further pursued.

Currently, non-nucleosidic polymerase inhibitors are further considered as components in multiclass DAA combination trials.

*Triple DAA combinations (a NS3/4A protease inhibitor, a NS5A inhibitor and a non-nucleoside polymerase inhibitor) ± RBV*

*ABT-450/r, ombitasvir and dasabuvir ± RBV*

Successful therapy with the triple DAA (“3D”) combination of ABT-450/r, ombitasvir and dasabuvir was first reported from the AVIATOR study (outlined above). SVR rates were 88–96% and 93–95% in treatment-naïve patients and patients with prior null response to PegIFN/RBV, respectively. SVR rates were lower in the RBV-free and the 8 week treatment arms. RBV dose reductions, however, did not significantly impact SVR rates. Also, baseline resistance variants did not impact treatment outcomes in HCV GT1a- and HCV GT1b-infected patients treated with 3 DAAs. One single HCV GT1b patient, who did not achieve SVR, did not have baseline resistance-associated variants in NS3, NS5A, or NS5B [47].

Results of the respective phase 3 program, comprising the studies SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II and PEARL-IV, PEARL-III, and PEARL-II were reported recently [48–52] (Table 4).

The placebo-controlled SAPPHIRE-I and SAPPHIRE-II trials investigated ABT-450/r-ombitasvir (150/100 mg–25 mg QD, available as single-tablet formulation) and dasabuvir (250 mg BID) with RBV for 12 weeks in treatment-naïve and experienced HCV genotype 1-infected patients without cirrhosis [48,49]. Overall, SVR rates were 96.2% and 96.3%, respectively (Table 4). SVR rates were high across subgroups (HCV GT1a and GT1b) as well as independent of prior treatment status. In both studies, rates of virologic failure were low. In SAPPHIRE-I, viral breakthrough or relapse occurred in 0.2% and 1.5% of the patients, respectively. All of the eight patients with virologic failure had one or more resistance associated variant(s) at the time of breakthrough or relapse. In SAPPHIRE-II, no virologic failure occurred during treatment. Seven patients had a viral relapse post treatment. Of those, five had at least one resistance-associated variant at the time of relapse. In both studies treatment was well tolerated, and treatment discontinuations due to adverse events were low (0.6% in SAPPHIRE-I, and 1% in SAPPHIRE-2). In SAPPHIRE-1, grade 1 or 2 haemoglobin reductions occurred in 47.5% and 5.8% of the patients, respectively. Haemoglobin levels of grade 2 and 3 were observed in 4.7% and 0.3% of the SAPPHIRE-II participants, respectively. Grade 3 or 4 hyperbilirubinaemia (SAPPHIRE-I: 2.4%, SAPPHIRE-II: 2.8%) was mostly transient and attributable to elevation of indirect bilirubin. None of these liver enzyme elevations met Hy’s law criteria.

The open-label TURQUOISE-II trial enrolled previously untreated and previously treated patients with compensated liver cirrhosis and randomized these patients to 12 vs. 24 weeks

**Table 4. Summary of selected clinical trials investigating triple DAA combinations (a NS3/4A protease inhibitor, a NSSA inhibitor and a non-nucleoside polymerase inhibitor) ± RBV.**

Sponsor	Trial name or NCT ID	Phase	DAA combination	RBV	Study population	Treatment (wk)	Outcome (SVR)
AbbVie	<b>AVIATOR</b>	2	ABT-450/r + ombitasvir + dasabuvir	± RBV	HCV GT1, naïve, prior null-responder, no cirrhosis	8, 12, 24	Naïve: 88-96% Null-responder: 93-95%
	<b>SAPPHIRE-I</b>	3	ABT-450/r—ombitasvir + dasabuvir	+ RBV	HCV GT1, naïve, no cirrhosis	12	Naïve 96.2%
	<b>SAPPHIRE-II</b>	3	ABT-450/r—ombitasvir + dasabuvir	+ RBV	HCV GT1, therapy experienced (relapse, partial-/null-responder), no cirrhosis	12	Experienced: 96.3%
	<b>TURQUOISE-II</b>	3	ABT-450/r—ombitasvir + dasabuvir	+ RBV	HCV GT1, naïve, experienced (relapse, partial-/null-responder), cirrhosis	12, 24	Overall: 91.8-95.9%
	<b>PEARL-IV</b>	3	ABT-450/r—ombitasvir + dasabuvir	± RBV	HCV GT1a, naïve, no cirrhosis	12	Naïve GT1 a 97.0 % (+ RBV); 90.2% (- RBV)
	<b>PEARL-III</b>	3	ABT-450/r—ombitasvir + dasabuvir	± RBV	HCV GT1b, naïve, no cirrhosis	12	Naïve, GT1b ~ 99.0%
	<b>PEARL-II</b>	3	ABT-450/r—ombitasvir + dasabuvir	± RBV	HCV GT1b, therapy experienced, no cirrhosis	12	Naïve GT1b, 97.0 % (+ RBV); 100% (- RBV)
	<b>M12-999</b>	2	ABT-450/r—ombitasvir + dasabuvir	+ RBV	HCV GT1, liver transplant recipients with recurrent infection	23	96.2%
Bristol-Myers-Squibb	<b>NCT01455090</b>	2	Asunaprevir + daclatasvir + BMS-791325	Ø RBV	HCV GT1, 4, naïve, ± cirrhosis	12, 24	Naïve, GT1 92% (70%, cirrhosis) Naïve, GT4: 100%
	<b>UNITY 1</b>	3	Asunaprevir + daclatasvir + BMS-791325	Ø RBV	HCV GT1, therapy naïve, no cirrhosis	12	Ongoing
	<b>UNITY 2</b>	3	Asunaprevir + daclatasvir + BMS-791325	Ø RBV	HCV GT1, therapy naïve, cirrhosis	12	Ongoing
	<b>UNITY 3 (Japan)</b>	3	Asunaprevir + daclatasvir + BMS-791325	Ø RBV	HCV GT1, therapy naïve ± cirrhosis	12	Ongoing
	<b>NCT01724086</b>	2	Simeprevir, GSK2336805, TMC647055 plus low-dose ritonavir	± RBV	HCV GT1, therapy experienced, no cirrhosis	12	Planned

of therapy (n = 208 and n = 172) with the above DAA combination ("3D") plus RBV [50]. Overall SVR rates were 91.8% (12 weeks) and 95.9% (24 weeks). SVR rates for HCV genotype 1 infected patients with prior null response were 80.0% (95% CI: 68.9–91.1) and 92.9% (95% CI: 85.1–100) for 12 and 24 weeks of treatment, respectively.

Virologic failure during treatment occurred in 0.5% of the patients in the 12-week group and in 1.7% of the patients in the 24-week group. Significantly less patients in the 24-week group than in the 12-week group had a relapse after treatment (0.6% vs. 5.9%). Seven of twelve patients (58.3%) who relapsed after 12 weeks of treatment had a HCV genotype 1a infection and a prior null response to treatment with PegIFN and RBV. Most patients had resistance associated variants at the time of virologic failure. Treatment was discontinued due to AEs in 2% of the patients. Grade 1 or 2 reductions in haemoglobin levels were common (grade 1 52.6%, grade 2 7.9%). Grade 3 and 4 haemoglobin abnormalities, however, occurred in only 0.8% and 0.3% of the patients, respectively. Grade 3 or 4 bilirubin elevations that mainly reflected elevations of indirect bilirubin were observed in 9.7% of the patients. There were no concomitant grade 3 or 4 aminotransferase abnormalities.

In the "3D" regimen, common adverse events were generally mild and, across the program, included e.g. pruritus, nausea, headache, diarrhoea, insomnia, and asthenia. In patients with cirrhosis, the safety and efficacy was similar compared to studies in non-cirrhotic patients.

The impact of addition of RBV to the "3D" combination was investigated in the PEARL-IV and PEARL-III studies that enrolled treatment-naïve HCV genotype 1a and HCV genotype 1b patients without cirrhosis, respectively [51]. Concomitant treatment with RBV was associated with higher response rates in HCV GT1a-infected patients (SVR [3D + RBV, n = 100]: 97.0% [95% CI: 93.7–100]; SVR [3D, n = 205]: 90.2% [95% CI: 86.2–94.3]) but not in patients with HCV genotype 1b infection (SVR [3D + RBV, n = 210]: 99.5%; SVR [3D, n = 209]: 99%).

The PEARL-II study included treatment-experienced patients with HCV genotype 1b infection who received 3D with and without RBV (n = 88 and n = 91 patients) [52]. Sustained virologic response rates were 97% and 100%, respectively.

Results of a phase 2 study that investigated the 3D regimen plus RBV in adult liver transplant recipients with recurrent HCV GT1 infection reported a SVR12 rate of 96.2% in this population [53]. No rejection, graft losses, or death was observed.

#### *Asunaprevir, daclatasvir and BMS-791325*

The interferon- and RBV free combination of asunaprevir (200 mg BID) and daclatasvir (60 mg QD) was investigated in combination with the non-nucleoside NS5B inhibitor BMS-791325 (75 or 150 mg BID) for 12 or 24 weeks in 66 treatment-naïve HCV genotype 1 infected patients without cirrhosis [54–56]. SVR12 rates were 92% and did not differ significantly by treatment duration [54]. Expansion cohorts of this trial comprised a larger number of previously untreated patients including those with liver cirrhosis, as well as HCV GT4 infected patients and patients who failed prior therapy with PegIFN and RBV.

Results of the expansion cohort evaluating this triple DAA regimen in a larger number (n = 166) of HCV genotype 1-infected patients were presented at AASLD 2013 [55]. Patients were treated for 12 weeks with asunaprevir (200 mg BID), daclatasvir

(30 mg QD) and two different doses of BMS-791325 ('325) (150 mg and 75 mg BID). Overall observed SVR12 rates were similar in the '325 150 mg and 75 mg groups (91.7% and 92.2%, respectively). In patients with liver cirrhosis 8/8 patients (100%) who received the '325 75 mg dose had a SVR, compared to 5/7 (70%) who received the 150 mg dose. SVR rates for n = 10 and n = 11 HCV genotype 4 patients who were treated for 12 weeks with this triple DAA combination and the two different BMS-791325 doses were 100% [56]. Results for treatment-experienced HCV genotype 1 patients are not yet available. Reported adverse events that occurred with a frequency of ≥10% comprised headache, asthenia, diarrhoea, and fatigue. Grade 3/4 laboratory abnormalities were reported in 6.3% and 1.3% percent for the pilot and extension cohorts, respectively. The phase 3 program, applying a twice-daily combination of daclatasvir, asunaprevir, and BMS-791325 (75 mg) is underway [57–59].

#### *Simeprevir, GSK2336805 and TMC647055/r ± RBV*

A pharmaceutical cross-collaboration investigating the NS3/4A protease inhibitor simeprevir in combination with the non-nucleoside polymerase inhibitor TMC647055 plus low-dose ritonavir with and without RBV and simeprevir plus TMC647055/r administered together with GSK2336805 without RBV is currently planned [60].

#### Host-targeting agents

In parallel to the development of DAAs, host factors associated with viral entry and replication were identified as drug targets. Up to now, two HTAs entered phase 2/3 clinical trials, the cyclophilin A inhibitor alisporivir, and miR-122 antagonist Miravirsin.

Cyclophilin A, a cellular enzyme with isomerase and chaperone activity, governs HCV replication and assembly via interaction with HCV NS5A and NS5B proteins. Alisporivir mediates its antiviral activity by directly binding to the enzymatic pocket of cyclophilin A. As cyclophilin A is relevant for HCV replication across genotypes and since it does not directly interact with viral proteins, alisporivir provides pan-genotypic activity and high barrier to resistance [61–63]. In 2012 the development program of alisporivir was set on hold due to safety concerns emerging from six severe cases of pancreatitis, including one death in the alisporivir/PegIFN combination trials. After extensive safety analyses, the interferon-free alisporivir development program was resumed. Currently, a phase 2 trial investigates response-guided therapy with alisporivir plus RBV for 12–24 weeks in treatment-naïve, HCV genotype 2/3-infected patients, however, results are not yet available.

The liver-specific micro-RNA miR-122 assures efficient replication of HCV-RNA, presumably by binding to HCV 5'-UTR, and thus protecting the viral RNA against cellular nucleases [64]. A recent phase 2 study tested the efficacy of the miR-122 antagonist miravirsin against placebo. Results showed a dose-dependent reduction of HCV-RNA of up to 3 log<sub>10</sub> IU per ml [65]. Given its only moderate antiviral effect in monotherapy, miravirsin still has to prove its potential in combination therapies. A phase 2 study that investigates the efficacy of miravirsin in combination with telaprevir and RBV in null-responders to prior therapy with PegIFN and RBV was initiated recently [66].



# Journal of Hepatology Update: Hepatitis C

## Summary

Laborious molecular research led to the characterization of the HCV life cycle and opened the gates for turbulent and eventful years in clinical drug development. The NS3/4A protease inhibitors telaprevir and boceprevir made the start, but were outpaced only two years after their approval by the availability of the nucleotide polymerase inhibitor sofosbuvir, offering the first interferon-free therapeutic option. Sustained virologic response rates, achieved with all-oral combination therapies, involving sofosbuvir in combination with a NS3/4A inhibitor or a NS5A inhibitor, certainly raise the bar but are challenged by competitive and also nearby available all-oral DAA combination therapies without a nucleotide polymerase inhibitors, as summarized herein. Also, the very good tolerability of the novel interferon-free DAA combination therapies now put the spotlight on RBV as undesirable combination partner. Also, it enables to progressively move clinical testing to previously difficult-to-cure populations, such as patients with decompensated liver cirrhosis, transplant-recipients and patients with end-stage renal disease. The development of fixed-dose formulations, reduced drug-drug interactions and shortened therapy durations (8–12 weeks) further facilitate the clinical applicability of the novel DAA regimens. With “perfect certainly not being the enemy of good” in today’s race towards all-oral interferon-free DAA combination therapies, trials investigating 4-week combination therapies are underway [67]. However, the dream of widely available antiviral HCV treatments is challenged by the reality of high costs, urgently requiring medical experts, pharmaceutical industry and health care policy makers to define the framework for the routine use of novel DAA combinations in clinical practice.

## Conflict of interest

T.M. Welzel, has consultancies for AbbVie, Boehringer-Ingelheim, Gilead, Janssen, and Novartis.

G. Dultz, has no conflict of interest with respect to this manuscript.

S. Zeuzem has consultancies for AbbVie, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead, Idenix Janssen, Merck, Novartis, Roche, Santaris, and Vertex.

## References

- [1] Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013;57:1333–1342.
- [2] Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol* 2013;10:553–562.
- [3] Lohmann V, Körner F, Koch J, Herian U, Theilmann L, Bartenschlager R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 1999;285:110–113.
- [4] Lohmann V, Bartenschlager R. On the history of hepatitis C virus cell culture systems. *J Med Chem* 2014;57:1627–1642.
- [5] Bartenschlager R, Lohmann V, Penin F. The molecular and structural basis of advanced antiviral therapy for hepatitis C virus infection. *Nat Rev Microbiol* 2013;11:482–496.
- [6] Pawlotsky (Guest Editor) JM. New hepatitis C therapies. *Semin Liver Dis* 2014;34:7–8.
- [7] Baugh JM, Garcia-Rivera JA, Gallay PA. Host-targeting agents in the treatment of hepatitis C: a beginning and an end? *Antiviral Res* 2013;100:555–561.
- [8] Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N Engl J Med* 2012;366:216–224.
- [9] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie Adrian M, Reddy KR, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405–2416.
- [10] Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364:2417–2428.
- [11] Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195–1206.
- [12] Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368:1878–1887.
- [13] Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368:1867–1877.
- [14] Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014;370:1993–2001.
- [15] Sulkowski M, Jacobson IM, Ghalib R, Rodriguez-Torres M, Younossi Z, Corregidor A, et al. Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 prior null responders with Metavir F0–2: COSMOS Study subgroup analysis. *J Hepatol* 2014;60:S4.
- [16] Lawitz E, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, Sulkowski MS, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype 1 prior null-responder/treatment-naïve patients (COSMOS study): primary endpoint (SVR12) results in patients with Metavir F3–4 (Cohort 2). *J Hepatol* 2014;60:S524.
- [17] Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014;370:211–221.
- [18] Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370:1889–1898.
- [19] Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;370:1483–1493.
- [20] Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014;370:1879–1888.
- [21] Gentile I, Buonomo AR, Borgia F, Zappulo E, Castaldo G, Borgia G. MK-5172: a second-generation protease inhibitor for the treatment of hepatitis C virus infection. *Expert Opin Investig Drugs* 2014;23:719–728.
- [22] Ng T, Reisch T, Middleton T, McDaniel K, Kempf D, Lu L, et al. ABT-493, a potent HCV NS3/4A protease inhibitor with broad genotype coverage. *Top Antivir Med* 2014;22:314.
- [23] Coburn CA, Meinke PT, Chang W, Fandozzi CM, Graham DJ, Hu B, et al. Discovery of MK-8742: an HCV NS5A inhibitor with broad genotype activity. *ChemMedChem* 2013;8:1930–1940.
- [24] Cheng C, Yu M, Peng B, Lee Y, Trejo-Martin A, Gong R, et al. 1191 GS-5816, a second generation HCV NS5A inhibitor with potent antiviral activity, broad genotypic coverage and a high resistance barrier. *J Hepatol* 2013;58:S484.
- [25] Walker J, Crosby R, Wang A, Wolde E, Vamathevan J, Vaitenleitner C, et al. Preclinical characterization of GSK2336805, a novel inhibitor of hepatitis C virus replication that selects for resistance in NS5A. *Antimicrob Agents Chemother* 2014;58:38–47.
- [26] Ng T, Krishnan P, Kati W, Reisch T, Lu L, Dekhtyar T, et al. ABT-530, an HCV NS5A inhibitor with potent pangenotypic activity and high barrier to resistance. *Top Antivir Med* 2014;22:315.
- [27] Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med* 2014;370:222–232.
- [28] Lawitz E, Hezode C, Varunok P, Thuluvath PJ, Baykal T, Kapoor M. Interferon- and ribavirin-free regimen of ABT-450/r + ABT-267 in HCV genotype 1b-infected treatment-naïve patients and prior null responders. *Hepatology* 2013;58:62A.
- [29] Hezode C, Marcellin P, Pol S, Hassanein T, Fleischer-Stepniewska K, Baykal T, et al. Results from the phase 2 PEARL-I study: interferon-free regimens of ABT-450/R + ABT-267 with or without ribavirin in patients with HCV genotype 4 infection. *J Hepatol* 2014;60:S24.
- [30] <http://www.clinicaltrials.gov/ct2/show/NCT02068222> [accessed on 30.08.14].
- [31] Muir A, Poordad F, Sheikh A, Elkashab M, Brennan R. SVR4 results for the combination of ACH-3102 and sovalprevir, with ribavirin, in subjects with genotype 1 chronic hepatitis C infection. *Hepatol Int* 2014;8:395.

- [32] <<http://ir.achillion.com/releasedetail.cfm?releaseid=853707>> [accessed on 03.08.14].
- [33] Suzuki Y, Ikeda K, Suzuki F, Toyota J, Karino Y, Chayama K, et al. Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options. *J Hepatol* 2013;58:655–662.
- [34] Lok AS, Gardiner DF, Hézode C, Lawitz EJ, Bourlière M, Everson GT, et al. Randomized trial of daclatasvir and asunaprevir with or without PegIFN/RBV for hepatitis C virus genotype 1 null responders. *J Hepatol* 2014;60:490–499.
- [35] Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014;59:2083–2091.
- [36] Manns M, Pol S, Jacobson I, Marcellin P, Gordon S, Peng C, et al. All-oral dual therapy with daclatasvir and asunaprevir in patients with HCV genotype 1b infection: phase 3 study results. *J Hepatol* 2014;60:S524.
- [37] Zeuzem S, Hezode C, Bronowicki JP, Loustad-Ratti V, Gea F, Buti M, et al. Daclatasvir in combination with simeprevir ± ribavirin for hepatitis C virus genotype 1 infection (Abstract 28LB). *Top Antivir Med* 2014;22:15–16.
- [38] A study of pharmacokinetics, efficacy, safety, tolerability, of the combination of simeprevir (TMC435), daclatasvir (BMS-790052), and ribavirin (RBV) in patients with recurrent chronic hepatitis C genotype 1b infection after orthotopic liver transplantation – Full text view – ClinicalTrials.gov: May 19, 2014; available from: <http://www.clinicaltrials.gov/ct2/show/NCT01938625>.
- [39] Lawitz E, Rodriguez-Torres M, Nguyen T, Sheikh A, Tobias H, Galati J, et al. A phase II study of samatasvir (IDX719) in combination with simeprevir and ribavirin in treatment naïve HCV-infected subjects with genotypes 1b and 4 (HELIX-1 study). *J Hepatol* 2014;60:S495.
- [40] Lawitz E, Vierling JM, Murillo A, Kugelmas M, Gerstoft J, Winkle P, et al. High efficacy and safety of the all-oral combination regimen, MK-5172/MK-8742 +/- RBV for 12 weeks in HCV genotype 1 infected patients: the C- WORTHY Study. *Hepatology* 2013;58:62A.
- [41] Hezode C, Serfaty L, Vierling JM, Kugelmas M, Pearlman B, Sievert W, et al. Safety and efficacy of the all-oral regimen of MK-5172/MK-8742 ± ribavirin in treatment-naïve, non-cirrhotic patients with hepatitis C virus genotype 1 infection: The C-WORTHY study. *J Hepatol* 2014;60:S5.
- [42] Lawitz E, Hezode C, Gane E, Tam E, Lagging M, Balart L, et al. Efficacy and safety of MK-5172 AND MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null-response: The C-WORTHY study. *J Hepatol* 2014;60:S25.
- [43] Search of: MK-5172 – List results – ClinicalTrials.gov: May 19, 2014; available from: <http://www.clinicaltrials.gov/ct2/results?term=MK-5172&Search=Search>.
- [44] Search of: MK-8742 – List results – ClinicalTrials.gov: May 19, 2014; available from: <http://www.clinicaltrials.gov/ct2/results?term=MK-8742&Search=Search>.
- [45] Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med* 2013;368:45–53.
- [46] Lawitz E, Poordad F, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. A phase 2a trial of 12-week interferon-free therapy with two direct-acting antivirals (ABT-450/r, ABT-072) and ribavirin in *IL28B* C/C patients with chronic hepatitis C genotype 1. *J Hepatol* 2013;59:18–23.
- [47] Krishnan P, Tripathi R, Irvin M, Beyer J, Reisch T, Schnell G, et al. Lack of impact of baseline resistance associated variants (RAVS) on treatment outcome in the aviator study with ABT-450/r, ABT-333, and ABT-267 +/- RBV. *J Hepatol* 2014;60:S498.
- [48] Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370:1594–1603.
- [49] Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370:1604–1614.
- [50] Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370:1973–1982.
- [51] Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014;370:1983–1992.
- [52] Andreone P, Colombo MG, Enejosa JV, Koksai I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014;147:359–365.
- [53] Kwo P, Mantry P, Coakley E, Te H, Vargas H, Brown R, et al. Results of the phase 2 study M12-999: interferon-free regimen of ABT-450/r/ABT-267 + ABT-333 + ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection. *J Hepatol* 2014;60:S47.
- [54] Everson GT, Sims KD, Rodriguez-Torres M, Hézode C, Lawitz E, Bourlière M, et al. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naïve patients with HCV genotype 1 infection. *Gastroenterology* 2014;146:420–429.
- [55] Everson GT, Sims KD, Thuluvath PJ, Lawitz E, Hassanein T, Rodriguez-Torres M, et al. LB-1: phase 2b study of the interferon-free and ribavirin-free combination of daclatasvir, asunaprevir, and BMS-791325 for 12 weeks in treatment-naïve patients with chronic HCV genotype 1 infection. *Hepatology* 2013;58:1377A.
- [56] Hassanein T, Sims K, Bennett M, Gitlin N, Lawitz E, Nguyen T, et al. All-oral therapy with daclatasvir in combination with asunaprevir and BMS-791325 for treatment-naïve patients with chronic HCV genotype 4 infection. *J Hepatol* 2014;60:S472.
- [57] UNITY 1: a study of an investigational treatment regimen of daclatasvir (DCV) + asunaprevir (ASV) + BMS-791325 in a fixed dose combination (the DCV 3DAA (direct acting antiviral) regimen) for 12 weeks for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection in non-cirrhotic subjects – Full text view – ClinicalTrials.gov: May 19, 2014; available from: <<http://www.clinicaltrials.gov/ct2/show/NCT01979939>>.
- [58] UNITY 2: a study of an investigational treatment regimen of DCV+ASV+BMS-791325 in a fixed dose combination (the DCV 3DAA (direct acting antiviral) regimen) with or without RBV for 12 weeks for the treatment of chronic hepatitis C virus(HCV)genotype 1 infection in subjects with compensated cirrhosis – Full text view – ClinicalTrials.gov: May 19, 2014; available from: <<http://www.clinicaltrials.gov/ct2/show/NCT01973049>>.
- [59] UNITY 3: a Japanese phase 3 study of a daclatasvir/asunaprevir/BMS-791325 in subjects with genotype 1 chronic hepatitis C – Full text view – ClinicalTrials.gov: May 19, 2014; available from: <<http://www.clinicaltrials.gov/ct2/show/NCT02123654>>.
- [60] A study to evaluate the safety, tolerability, and effectiveness of a 12-week combination therapy of TMC647055 and TMC435 with and without gsk23336805 with a pharmacokinetic enhancer with and without ribavirin in patients infected with chronic genotype 1 hepatitis C virus – Full text view – ClinicalTrials.gov: May 19, 2014; available from: <<http://www.clinicaltrials.gov/ct2/show/NCT01724086>>.
- [61] Paeshuyse J, Kaul A, de Clercq E, Rosenwirth B, Dumont J, Scalfaro P, et al. The non-immunosuppressive cyclosporin DEBIO-025 is a potent inhibitor of hepatitis C virus replication in vitro. *Hepatology* 2006;43:761–770.
- [62] Chatterji U, Bobardt M, Selvarajah S, Yang F, Tang H, Sakamoto N, et al. The isomerase active site of cyclophilin A is critical for hepatitis C virus replication. *J Biol Chem* 2009;284:16998–17005.
- [63] Coelmont L, Kaptein S, Paeshuyse J, Vliegen I, Dumont J, Vuagniaux G, et al. Debio 025, a cyclophilin binding molecule, is highly efficient in clearing hepatitis C virus (HCV) replicon-containing cells when used alone or in combination with specifically targeted antiviral therapy for HCV (STAT-C) inhibitors. *Antimicrob Agents Chemother* 2009;53:967–976.
- [64] Thibault PA, Wilson JA. Targeting miRNAs to treat hepatitis C virus infections and liver pathology: inhibiting the virus and altering the host. *Pharmacol Res* 2013;75:48–59.
- [65] Janssen Harry LA, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, et al. Treatment of HCV infection by targeting microRNA. *N Engl J Med* 2013;368:1685–1694.
- [66] Miraviren in combination with telaprevir and ribavirin in null responder to pegylated-interferon alpha plus ribavirin subjects with chronic hepatitis C virus infection – Full text view – ClinicalTrials.gov: April 27, 2014; available from: <<http://clinicaltrials.gov/ct2/show/NCT01872936>>.
- [67] Efficacy and safety of MK-5172, MK-8742, and Sofosbuvir for chronic infection with hepatitis C virus genotypes 1 and 3 (MK-5172-074) – Full text view – ClinicalTrials.gov: May 21, 2014; available from: <<http://www.clinicaltrials.gov/ct2/show/NCT02133131>>.