

A SPECIAL MEETING REVIEW EDITION

Advances in the Treatment of Hepatitis C Virus Infection From EASL 2014

The 49th Annual Meeting of the European Association for the Study of the Liver • April 9-13, 2014 • London, United Kingdom

Special Reporting on:

- SAPPHERE II: Phase 3 Placebo-Controlled Study of Interferon-Free, 12-Week Regimen of ABT-450/R/ABT-267, ABT-333, and Ribavirin in Treatment-Experienced Adults With Hepatitis C Virus Genotype 1
- All Oral Fixed-Dose Combination Sofosbuvir/Ledipasvir With or Without Ribavirin for 12 or 24 Weeks in Treatment-Naive Genotype 1 HCV-Infected Patients: the Phase 3 ION-1 Study
- PEARL-III: 12 Weeks of ABT-450/R/267 + ABT-333 Achieved SVR in >99% of 419 Treatment-Naive HCV Genotype 1B-Infected Adults With or Without Ribavirin
- 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
- Sofosbuvir and Ribavirin for the Treatment of Chronic HCV With Cirrhosis and Portal Hypertension With and Without Decompensation: Early Virologic Response and Safety
- All-Oral Dual Therapy With Daclatasvir and Asunaprevir in Patients With HCV Genotype 1B Infection: Phase 3 Study Results
- Sofosbuvir/Ledipasvir Fixed Dose Combination Is Safe and Effective in Difficult-to-Treat Populations Including Genotype-3 Patients, Decompensated Genotype-1 Patients, and Genotype-1 Patients With Prior Sofosbuvir Treatment Experience
- Sofosbuvir and Ribavirin for the Treatment of Recurrent Hepatitis C Infection After Liver Transplantation: Results of a Prospective, Multicenter Study

PLUS Meeting Abstract Summaries

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ON THE WEB:

gastroenterologyandhepatology.net



In the treatment of HCV

ADVANCING WHAT'S POSSIBLE



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INDICATION

SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) as a component of a combination antiviral treatment regimen.

- SOVALDI efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection

Prescribing Considerations:

- Monotherapy of SOVALDI is not recommended.
- Treatment regimen and duration are dependent on both viral genotype and patient population.
- Treatment response varies based on baseline host and viral factors.

CHANGE THE WAY YOU TREAT HCV GT 1 PATIENTS

A 12-week regimen of SOVALDI + Peg-IFN + RBV delivered high cure (SVR) rates for GT 1 patients^{1,a}

- Overall response in treatment-naïve subjects with GT 1, 4, 5 and 6 was 90%¹
- SVR12 was 89% in treatment-naïve GT 1 subjects taking SOVALDI + Peg-IFN + RBV for just 12 weeks¹
- Treatment-experienced GT 1 patients can be treated with SOVALDI + Peg-IFN + RBV for 12 weeks, with an estimated SVR of 71%^{1,b}
- The most common adverse events (incidence $\geq 20\%$, all grades) observed with SOVALDI + Peg-IFN + RBV were fatigue, headache, nausea, insomnia and anemia¹
- The discontinuation rate due to adverse events was 2% in NEUTRINO¹

^aSustained virologic response (SVR) was the primary endpoint, which was defined as HCV RNA < 25 IU/mL at 12 weeks after the end of treatment.¹ Achieving SVR is considered a virologic cure.²

^bThe response rate in treatment-naïve subjects with difficult-to-treat factors (n=52) may approximate the response rate in patients who previously failed pegylated interferon and ribavirin therapy. (Difficult-to-treat factors include GT 1 subjects with IL28B non-C/C alleles, HCV RNA $> 800,000$ IU/mL and Metavir F3/F4 fibrosis.)¹

NEUTRINO—GT 1, 4, 5 and 6 treatment-naïve adult subjects¹

An open-label, single-arm trial evaluating 12 weeks of treatment with SOVALDI in combination with peginterferon alfa 2a (Peg-IFN) and ribavirin (RBV) in treatment-naïve subjects (N=327) with genotype 1, 4, 5 or 6 HCV infection.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SOVALDI combination treatment with ribavirin or with peginterferon alfa plus ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant because of the risk for birth defects and fetal death associated with ribavirin. Contraindications to peginterferon alfa and ribavirin also apply to SOVALDI combination treatment. Refer to the prescribing information of peginterferon alfa and ribavirin for a list of their contraindications.

WARNINGS AND PRECAUTIONS

- **Pregnancy: Use with Ribavirin or Peginterferon Alfa/Ribavirin:** Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners must use 2 forms of non-hormonal contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Refer to the prescribing information for ribavirin.
- **Use with Potent P-gp Inducers:** Rifampin and St. John's wort should not be used with SOVALDI as they may significantly decrease sofosbuvir plasma concentration, reducing its therapeutic effect.

Please see Brief Summary of full Prescribing Information on the following pages.

sovaldi.com/hcp





Dosing information for patients with HCV GT 1 or 4¹

- The recommended regimen and treatment duration for SOVALDI combination therapy in HCV GT 1 and 4 mono-infected and HCV/HIV-1 co-infected patients is SOVALDI 400 mg (one tablet, taken orally, once daily with or without food) + Peg-IFN alfa^a + RBV^b for 12 weeks¹
- No response-guided therapy is required with SOVALDI¹
- 24 weeks of SOVALDI + RBV is the first approved all-oral regimen that can be considered for HCV GT 1 patients who are ineligible to receive an IFN-based regimen¹
- If the other agents used in combination with SOVALDI are permanently discontinued, SOVALDI should also be discontinued¹
- No SOVALDI dose adjustments are necessary based on advanced age, race, mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m²) or mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, or C). The safety and efficacy of SOVALDI have not been established in patients with severe renal impairment, end stage renal disease (ESRD) or decompensated cirrhosis¹
- If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dose should be reduced or discontinued. Refer to the peginterferon alfa and ribavirin prescribing information for additional information about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dose¹

^aSee peginterferon alfa prescribing information for dosing recommendation for patients with genotype 1 or 4 CHC.

^bDose of ribavirin is weight-based (<75 kg = 1000 mg and ≥ 75 kg = 1200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤ 50 mL/min) require ribavirin dose reduction; refer to ribavirin prescribing information.

IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

Most common ($\geq 20\%$, all grades) adverse reactions for:

- SOVALDI + peginterferon alfa + ribavirin combination therapy were fatigue, headache, nausea, insomnia, and anemia
- SOVALDI + ribavirin combination therapy were fatigue and headache

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of SOVALDI is not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of sofosbuvir, reducing its therapeutic effect.

Please see Brief Summary of full Prescribing Information on the following pages.



SOVALDI® (sofosbuvir)

Brief summary of full Prescribing Information. Please see full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) as a component of a combination antiviral treatment regimen.

• SOVALDI efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection

Prescribing considerations:

- Monotherapy of SOVALDI is not recommended
- Treatment regimen and duration are dependent on both viral genotype and patient population
- Treatment response varies based on baseline host and viral factors

DOSAGE AND ADMINISTRATION: Adult Dosage: one 400 mg tablet, taken orally, once daily with or without food. SOVALDI should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for treatment of CHC in adults.

Recommended dose and treatment duration for SOVALDI combination therapy for patients with: genotype 1 or 4 CHC is SOVALDI + peginterferon alfa + ribavirin for 12 weeks; genotype 2 CHC is SOVALDI + ribavirin for 12 weeks; and genotype 3 CHC is SOVALDI + ribavirin for 24 weeks. See peginterferon alfa prescribing information for dosing recommendation for patients with genotype 1 or 4 CHC. Dose of ribavirin is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg). Daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤50 mL/min) require ribavirin dose reduction; refer to ribavirin prescribing information.

SOVALDI in combination with ribavirin for 24 weeks can be considered as a therapeutic option for CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen. Treatment decision should be guided by assessment of potential benefits and risks for individual patient.

Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation: SOVALDI in combination with ribavirin is recommended for up to 48 weeks or until time of liver transplantation to prevent post-transplant HCV reinfection.

Dose Modification: Dose reduction of SOVALDI is not recommended.

Genotype 1 and 4: If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dose should be reduced or discontinued. Refer to peginterferon alfa and ribavirin prescribing information for additional information about how to reduce and/or discontinue peginterferon alfa and/or ribavirin dose. **Genotype 2 and 3:** If a patient has a serious adverse reaction potentially related to ribavirin, ribavirin dose should be modified or discontinued, if appropriate, until adverse reaction abates or decreases in severity.

Ribavirin dose modification guideline for coadministration with SOVALDI: Reduce the ribavirin dose to 600 mg/day^a in patients with no cardiac disease if hemoglobin is <10 g/dL and discontinue ribavirin^b if it is <8.5 g/dL. Reduce the ribavirin dose to 600 mg/day^a in patients with history of stable cardiac disease who have ≥2 g/dL decrease in hemoglobin during any 4 week treatment period and discontinue ribavirin^b if it is <12 g/dL despite 4 weeks at reduced dose.^b Daily dose of ribavirin is administered orally in two divided doses with food.^b Once ribavirin has been withheld due to either laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase dose to 800 mg daily. It is not recommended that ribavirin be increased to original assigned dose (1000 mg to 1200 mg daily). **Discontinuation of Dosing:** If other agents used in combination with SOVALDI are permanently discontinued, SOVALDI should also be discontinued.

Severe Renal Impairment and End Stage Renal Disease: No dose recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m²) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

CONTRAINDICATIONS: When SOVALDI is used in combination with ribavirin or peginterferon alfa/ribavirin, contraindications applicable to those agents are applicable to combination therapies. Refer to prescribing information of peginterferon alfa and ribavirin for a list of their contraindications. SOVALDI combination treatment with ribavirin or peginterferon alfa/ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant because of the risks for birth defects and fetal death associated with ribavirin.

WARNINGS AND PRECAUTIONS:

Pregnancy: Use with Ribavirin or Peginterferon Alfa/Ribavirin: Ribavirin may cause birth defects and/or death of the exposed fetus and animal studies have shown that interferons have abortifacient effects. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. When SOVALDI is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. There are no data on the effectiveness of systemic hormonal contraceptives in women taking SOVALDI, therefore, two non-hormonal methods of contraception should be used during treatment with SOVALDI and concomitant ribavirin. Refer also to the prescribing information for ribavirin.

Use with Potent P-gp Inducers: Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of SOVALDI. Rifampin and St. John's wort should not be used with SOVALDI.

ADVERSE REACTIONS: Adverse Reactions from Clinical Trials Experience: SOVALDI should be administered with ribavirin or peginterferon alfa/ribavirin. Refer to the prescribing information of peginterferon alfa and ribavirin for a description of adverse reactions associated with their use. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety assessment of SOVALDI is based on pooled Phase 3 clinical trial data (both controlled and uncontrolled) including 650 subjects who received SOVALDI + ribavirin combination therapy for 12 weeks, 98 subjects who received SOVALDI + ribavirin combination therapy for 16 weeks, 250 subjects who received SOVALDI + ribavirin combination therapy for 24 weeks, 327 subjects who received SOVALDI + peginterferon alfa + ribavirin combination therapy for 12 weeks, 243 subjects who received peginterferon alfa + ribavirin for 24 weeks and 71 subjects who received placebo (PBO) for 12 weeks. The proportion of subjects who permanently discontinued treatment due to adverse events was 4% for subjects receiving placebo, 1% for subjects receiving SOVALDI + ribavirin for 12 weeks, <1% for subjects receiving SOVALDI + ribavirin for 24 weeks, 11% for subjects receiving peginterferon alfa + ribavirin for 24 weeks and 2% for subjects receiving SOVALDI + peginterferon alfa + ribavirin for 12 weeks. Treatment-emergent adverse events observed in ≥15% of subjects in clinical trials are provided in Table 1. A side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs. The most common adverse events (≥ 20%) for SOVALDI + ribavirin combination therapy were fatigue and headache. The most common adverse events (≥ 20%) for SOVALDI + peginterferon alfa + ribavirin combination therapy were fatigue, headache, nausea, insomnia and anemia.

Table 1 Treatment-Emergent Adverse Events (All Grades) Reported in ≥15% of Subjects in Any Treatment Arm

	Interferon-free Regimens			Interferon-containing Regimens	
	PBO 12 weeks	SOVALDI + RBV ^a 12 weeks	SOVALDI + RBV ^a 24 weeks	Peg-IFN alfa + RBV ^b 24 weeks	SOVALDI + Peg-IFN alfa + RBV ^b 12 weeks
	N=71	N=650	N=250	N=243	N=327
Fatigue	24%	38%	30%	55%	59%
Headache	20%	24%	30%	44%	36%
Nausea	18%	22%	13%	29%	34%
Insomnia	4%	15%	16%	29%	25%
Pruritus	8%	11%	27%	17%	17%
Anemia	0%	10%	6%	12%	21%
Asthenia	3%	6%	21%	3%	5%
Rash	8%	8%	9%	18%	18%
Decreased Appetite	10%	6%	6%	18%	18%
Chills	1%	2%	2%	18%	17%
Influenza Like Illness	3%	3%	6%	18%	16%
Pyrexia	0%	4%	4%	14%	18%
Diarrhea	6%	9%	12%	17%	12%
Neutropenia	0%	<1%	<1%	12%	17%
Myalgia	0%	6%	9%	16%	14%
Irritability	1%	10%	10%	16%	13%

^a Subjects received weight-based ribavirin (1000 mg per day if weighing <75 kg or 1200 mg per day if weighing ≥75 kg).

^b Subjects received 800 mg ribavirin per day regardless of weight.

With the exception of anemia and neutropenia, the majority of events presented in Table 1 occurred at severity of grade 1 in SOVALDI-containing regimens.

Less Common Adverse Reactions Reported in Clinical Trials (<1%): The following ADRs occurred in <1% of subjects receiving SOVALDI in a combination regimen in any one trial. These events have been included because of their seriousness or assessment of potential causal relationship. **Hematologic Effects:** pancytopenia (particularly in subjects receiving concomitant pegylated interferon).

Psychiatric Disorders: severe depression (particularly in subjects with pre-existing history of psychiatric illness), including suicidal ideation and suicide.

Laboratory Abnormalities: Changes in selected hematological parameters are described in Table 2. A side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

Brief Summary (cont.)

Table 2 Percentage of Subjects Reporting Selected Hematological Parameters

Hematological Parameters	Interferon-free Regimens			Interferon-containing Regimens	
	PBO 12 weeks	SOVALDI + RBV ^a 12 weeks	SOVALDI + RBV ^a 24 weeks	Peg-IFN + RBV ^b 24 weeks	SOVALDI + Peg-IFN + RBV ^a 12 weeks
	N=71	N=647	N=250	N=242	N=327
Hemoglobin (g/dL)					
<10	0	8%	6%	14%	23%
<8.5	0	1%	<1%	2%	2%
Neutrophils (x10 ⁹ /L)					
≥0.5 - <0.75	1%	<1%	0	12%	15%
<0.5	0	<1%	0	2%	5%
Platelets (x10 ⁹ /L)					
≥25 - <50	3%	<1%	1%	7%	<1%
<25	0	0	0	0	0

^a Subjects received weight-based ribavirin (1000 mg per day if weighing <75 kg or 1200 mg per day if weighing ≥75 kg).

^b Subjects received 800 mg ribavirin per day regardless of weight.

Bilirubin Elevations: Total bilirubin elevation of more than 2.5xULN was observed in none of the subjects in the SOVALDI + peginterferon alfa + ribavirin 12 weeks group and in 1%, 3% and 3% of subjects in the peginterferon alfa + ribavirin 24 weeks, SOVALDI + ribavirin 12 weeks and SOVALDI + ribavirin 24 weeks groups, respectively. Bilirubin levels peaked during the first 1 to 2 weeks of treatment and subsequently decreased and returned to baseline levels by post-treatment Week 4. These bilirubin elevations were not associated with transaminase elevations.

Creatine Kinase Elevations: Creatine kinase was assessed in the FISSION and NEUTRINO trials. Isolated, asymptomatic creatine kinase elevation of greater than or equal to 10xULN was observed in <1%, 1% and 2% of subjects in the peginterferon alfa + ribavirin 24 weeks, SOVALDI + peginterferon alfa + ribavirin 12 weeks and SOVALDI + ribavirin 12 weeks groups, respectively.

Lipase Elevations: Isolated, asymptomatic lipase elevation of greater than 3xULN was observed in <1%, 2%, 2%, and 2% of subjects in the SOVALDI + peginterferon alfa + ribavirin 12 weeks, SOVALDI + ribavirin 12 weeks, SOVALDI + ribavirin 24 weeks and peginterferon alfa + ribavirin 24 weeks groups, respectively.

DRUG INTERACTIONS: Potential for Drug Interactions: After oral administration of SOVALDI, sofosbuvir is rapidly converted to the predominant circulating metabolite GS-331007 that accounts for greater than 90% of drug related material systemic exposure, while the parent sofosbuvir accounts for approximately 4% of drug related material. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses. Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Drugs that are potent P-gp inducers in the intestine (e.g., rifampin or St. John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of SOVALDI and thus should not be used with SOVALDI. Coadministration of SOVALDI with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration; accordingly, SOVALDI may be coadministered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of drugs that are substrates of these transporters. The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity and high capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant drugs.

Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction: Drug interaction information for SOVALDI with potential concomitant drugs is summarized as follows and the list is not inclusive. The drug interactions described are based on potential drug interactions that may occur with SOVALDI.

Anticonvulsants: Coadministration of SOVALDI with carbamazepine, phenytoin, phenobarbital, oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended. **Antimycobacterials:** Coadministration of SOVALDI with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended. SOVALDI should not be used with rifampin, a potent intestinal P-gp. **Herbal Supplements:** SOVALDI should not be used with St. John's wort (*Hypericum perforatum*), a potent intestinal P-gp inducer. **HIV Protease Inhibitors:** Coadministration of SOVALDI with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with SOVALDI: In addition to the drugs listed above, the interaction between SOVALDI and the following drugs was evaluated in clinical trials and no dose adjustment is needed for either drug: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category X: Use with Ribavirin and/or Peginterferon Alfa/Ribavirin: Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using two forms of effective contraception during treatment with ribavirin and for 6 months after treatment has concluded. There are no data on the effectiveness of systemic hormonal contraceptives in women taking SOVALDI. Therefore, two effective non-hormonal methods of contraception should be used during treatment with SOVALDI and concomitant ribavirin. **In case of exposure during pregnancy, a Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Healthcare providers and patients are encouraged to report such cases by calling Ribavirin Pregnancy Registry at 1-800-593-2214. For patients who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals, an Antiretroviral Pregnancy Registry is also available at 1-800-258-4263.**

Animal Data: Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans.

Pregnancy Category B: SOVALDI: There are no adequate and well-controlled studies with SOVALDI in pregnant women.

Animal Data: No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure to the predominant circulating metabolite GS-331007 increased over the course of gestation from approximately 5 to 10-fold and 12 to 28-fold the exposure in humans at the recommended clinical dose, respectively.

Nursing Mothers: It is not known whether SOVALDI and its metabolites are present in human breast milk. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats, without effect on nursing pups. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with ribavirin containing regimens, taking into account the importance of the therapy to the mother. See also the prescribing information for ribavirin.

Pediatric Use: Safety and effectiveness of SOVALDI in children less than 18 years of age have not been established.

Geriatric Use: Clinical studies of SOVALDI included 90 subjects aged 65 and over. The response rates observed for subjects over 65 years of age were similar to that of younger subjects across treatment groups. No dose adjustment of SOVALDI is warranted in geriatric patients.

Renal Impairment: No dose adjustment of SOVALDI is required for patients with mild or moderate renal impairment. The safety of SOVALDI has not been assessed in patients with severe renal impairment (eGFR <30 mL/min/1.73m²) or end stage renal disease (ESRD) requiring hemodialysis. Refer also to ribavirin prescribing information for patients with CrCl<50 mL/min.

Hepatic Impairment: No dose adjustment of SOVALDI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of SOVALDI have not been established in patients with decompensated cirrhosis. See peginterferon alfa prescribing information for contraindication in hepatic decompensation.

Patients with HCV/HIV-1 Co-infection: The safety and efficacy of SOVALDI was assessed in 223 HCV/HIV-1 co-infected subjects. See Dosage and Administration for dosing recommendations in HCV/HIV-1 co-infected patients. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. Elevated total bilirubin (grade 3 or 4) was observed in 30/32 (94%) subjects receiving atazanavir as part of the antiretroviral regimen. None of the subjects had concomitant transaminase increases. Among subjects not taking atazanavir, grade 3 or 4 elevated total bilirubin was observed in 2 (1.5%) subjects, similar to the rate observed with HCV mono-infected subjects receiving SOVALDI + ribavirin in Phase 3 trials.

Patients with Hepatocellular Carcinoma (HCC) Awaiting Liver Transplantation: SOVALDI was studied in HCV-infected subjects with HCC prior to undergoing liver transplantation in an open-label clinical trial evaluating the safety and efficacy of SOVALDI and ribavirin administered pre-transplant to prevent post-transplant HCV reinfection. See Dosage and Administration for dosing recommendations in patients with HCC awaiting liver transplantation. The safety profile of SOVALDI and ribavirin in HCV-infected subjects prior to liver transplantation was comparable to that observed in subjects treated with SOVALDI and ribavirin in Phase 3 clinical trials.

Post-Liver Transplant Patients: The safety and efficacy of SOVALDI have not been established in post-liver transplant patients.

CHC Patients with Genotype 5 or 6 HCV Infection: Available data on subjects with genotype 5 or 6 HCV infection are insufficient for dosing recommendations.

References: 1. SOVALDI [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; December 2013. 2. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54:1433-1444.



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SAPPHIRE II: Phase 3 Placebo-Controlled Study of Interferon-Free, 12-Week Regimen of ABT-450/R/ABT-267, ABT-333, and Ribavirin in Treatment-Experienced Adults With Hepatitis C Virus Genotype 1

The randomized, double-blind, placebo-controlled, phase 3 SAPPHIRE trials explored a 3-drug combination in patients with noncirrhotic, genotype 1 hepatitis C virus (HCV) who were either treatment-naïve (SAPPHIRE-I) or treatment-experienced (SAPPHIRE-II). The drug combination was designed to inhibit 3 points of the viral life cycle and consisted of a single-tablet coformulation of the protease inhibitor ABT-450 (150 mg) with ritonavir (100 mg) as a booster, plus the NS5A inhibitor ombitasvir (25 mg) and the nonnucleoside NS5B polymerase inhibitor dasabuvir (250 mg twice daily). ABT-450 is a potent inhibitor of NS3 and NS4A proteases. Combination with ritonavir increases the peak, trough, and overall exposure of ABT-450 while enabling once-daily dosing. Patients also received ribavirin (1000-1200 mg daily). In both trials, patients were randomized 3:1 to receive either the active drugs or matched placebo during a 12-week double-blind period. Patients initially randomized to the placebo arm then received open-label treatment with the “3D” regimen plus ribavirin for 12 weeks. The primary endpoint of both trials was sustained virologic response at week 12 (SVR12). The primary efficacy analysis compared the SVR12 rate in patients receiving the active regimen with a historical response rate observed in a similar group of patients who had received retreatment with telaprevir and pegylated interferon- α plus ribavirin.

SAPPHIRE-II

SAPPHIRE-II (A Randomized, Double-Blind, Placebo-Controlled Study

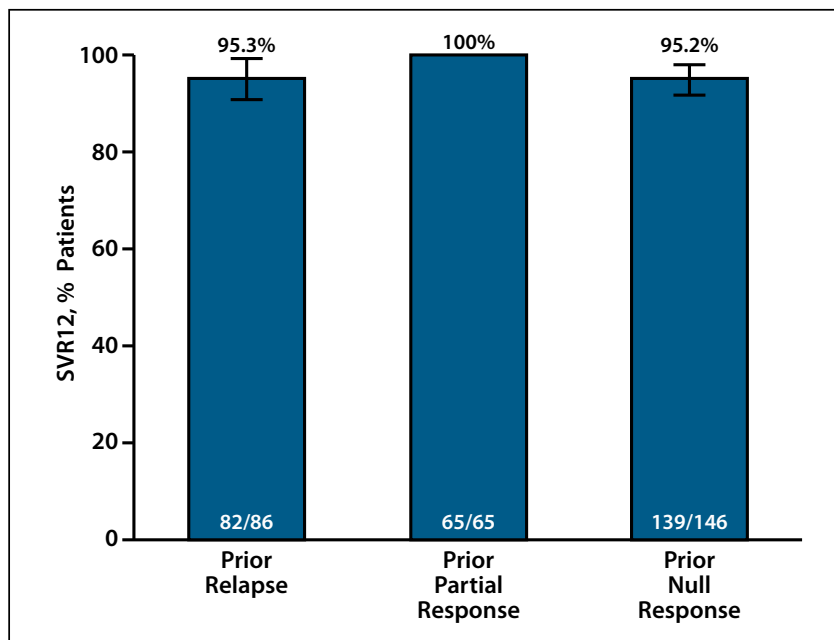


Figure 1. SVR12 rates in the SAPPHIRE-II trial. SAPPHIRE-II, A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/R/ABT-267) and ABT-333 Co-Administered With Ribavirin [RBV] in Treatment-Experienced Adults With Genotype 1 Chronic Hepatitis C Virus [HCV] Infection; SVR12, sustained virologic response at week 12. Adapted from Zeuzem S et al. EASL abstract O1. *J Hepatol.* 2014;60(suppl 1):S1.¹

to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 [ABT-450/R/ABT-267] and ABT-333 Co-Administered With Ribavirin [RBV] in Treatment-Experienced Adults With Genotype 1 Chronic Hepatitis C Virus [HCV] Infection) enrolled 394 patients previously treated with pegylated interferon- α and ribavirin who relapsed or demonstrated a partial or null response.^{1,2} Approximately two-thirds of patients had fibrosis stage F0 or F1, approximately 90% of patients had the interleukin 28B (*IL28B*) non-CC genotype, and nearly 60% of patients had HCV subtype 1a. The 297 evaluable patients treated with the active regimen yielded an SVR12 rate of 96.3% (95% CI, 94.2%-98.4%),

which was both noninferior and superior to the historic control rate of 65%. SVR12 rates were 95.3% (82 of 86 patients) for patients with prior relapse, 100% (65 of 65 patients) for patients with a prior partial response, and 95.2% (139 of 146 patients) for patients who failed to respond to prior treatment (Figure 1). The HCV subgenotype did not significantly influence response rates. Although no virologic breakthroughs occurred for patients on active treatment, 7 of 297 patients (2.4%) relapsed at post-treatment week 2 (n=2), 4 (n=3), or 8 (n=2), and resistance-associated variants were detected in 5 of these patients. Pruritus was more frequent in patients receiving active treatment vs

ABSTRACT SUMMARY TURQUOISE-II: SVR12 Rates of 92–96% in 380 Hepatitis C Virus Genotype 1–Infected Adults With Compensated Cirrhosis Treated With ABT-450/R/ABT-267 and ABT-333 Plus Ribavirin (3D+RBV)

HCV patients with cirrhosis were excluded from phase 3 studies of the 3D regimen, including SAPPHIRE-I, SAPPHIRE-II, and PEARL-III. To address treatment needs for these patients, the open-label, phase 3 TURQUOISE-II (A Study to Evaluate the Safety and Effect of ABT-450, Ritonavir and ABT-267 [ABT-450/R/ABT-267] and ABT-333 Coadministered With Ribavirin [RBV] in Hepatitis C Virus [HCV] Genotype 1–Infected Adults With Compensated Cirrhosis) study enrolled HCV genotype 1 patients with Child-Turcotte-Pugh (CTP) class A cirrhosis and randomized them to receive 12 weeks (n=208) or 24 weeks (n=172) of treatment with the 3D com-

ination (ABT-450 [150 mg], ritonavir [100 mg], and ombitasvir [25 mg]) daily, plus dasabuvir (250 mg twice daily) and ribavirin administered according to body weight (Abstract O163; Poordad F et al. *N Engl J Med.* 2014;370(21):1973–1982). Fifty-nine percent of patients had received prior treatment, 36% were previous null responders, and 18% had a CTP score greater than 5. SVR12 rates for 12 weeks vs 24 weeks of treatment were 91.8% (95% CI, 87.6%–96.1%) and 95.9% (95% CI, 92.6%–99.3%), respectively. These rates are superior to the historic control rate of 47% with a telaprevir-based regimen, and established both noninferiority and superiority of the 3D

regimen in cirrhotic patients. Patients harboring HCV genotype 1a who experienced a null response from prior treatment demonstrated an improvement in response with the longer 3D regimen, with SVR12 rates of 80% for 12 weeks of treatment vs 92.9% for 24 weeks. In contrast, patients with HCV genotype 1b infection and prior null response had an SVR12 rate of 100% with either treatment duration, whereas other genotype 1a subgroups achieved SVR12 rates of 92% to 100% with either 12 or 24 weeks of treatment. The study treatment was well tolerated, with 1.9% to 2.3% of patients in the 2 arms discontinuing owing to an AE.

placebo (13.8% vs 5.2%; $P=.03$), and 3 patients receiving the study drugs discontinued treatment owing to adverse events (AEs). Grade 3 hemoglobin values were observed in 0.3% of patients receiving active treatment.

SAPPHIRE-I

SAPPHIRE-I (A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 [ABT-450/R/ABT-267] and ABT-333 Coadministered With Ribavirin [RBV] in Treatment-Naïve Adults With Genotype 1 Chronic Hepatitis C Virus [HCV] Infection) invoked the same study design but randomized treatment-naïve patients without cirrhosis to receive either the study drug combination (n=473) or placebo (n=158).^{3,4}

Approximately three-fourths of patients had fibrosis stage F0 or F1, nearly 70% of patients had the *IL28B* non-CC genotype, and approximately two-thirds of patients had HCV subtype 1a. The SVR12 rate for the 473 patients who initially received active drugs was 96.2% (95% CI, 94.5%–97.9%) and was superior to the calculated historic control rate of 78%. Also in the active treatment arm, response rates for patients with HCV genotype 1a or 1b infection were 95.3% (307 of 322 patients) and 98.0% (148 of 151 patients), respectively, both demonstrating superiority to the historic control rate. Virologic failure occurred in 7 patients with HCV genotype 1a and in 1 patient with genotype 1b. One patient experienced on-treatment breakthrough. Three patients relapsed at week 2, another 3 at week 8, and 1 at week 12. The rate of discontinuation

was 0.6% in both the active treatment and control arms. AEs that occurred in significantly more patients in the active treatment arm included nausea, pruritus, insomnia, diarrhea, and asthenia ($P<.05$ for each). All hemoglobin reductions were grade 1 or 2.

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All Oral Fixed-Dose Combination Sofosbuvir/Ledipasvir With or Without Ribavirin for 12 or 24 Weeks in Treatment-Naive Genotype 1 HCV-Infected Patients: the Phase 3 ION-1 Study

A single pill formulated to deliver 2 compounds directed against the HCV NS5A and NS5B proteases was evaluated in the phase 3 ION studies. All 3 trials evaluated regimens containing a once-daily, fixed-dose combination (FDC) pill consisting of 2 direct-acting antiviral agents: the NS5B nucleotide polymerase inhibitor sofosbuvir (400 mg) and the NS5A inhibitor ledipasvir (90 mg). Sofosbuvir previously demonstrated clinical activity in HCV genotypes 1 through 6 with a high barrier to the development of treatment-resistant HCV mutants.¹ It is currently approved as a once-daily, oral 400 mg tablet in combination with other agents for treating chronic HCV infection. Ledipasvir is an investigational drug that has shown picomolar potency against HCV genotypes 1a and 1b.² ION-1 (A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination [FDC] +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects With Chronic Genotype 1 HCV Infection) and ION-2 (Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV) compared 12 weeks vs 24 weeks of the sofosbuvir/ledipasvir FDC pill with or without ribavirin. ION-1 enrolled treatment-naive patients, and ION-2 enrolled treatment-experienced patients. ION-3 tested the 2-drug combination with or without ribavirin for 8 weeks and included a third arm administering the FDC combination alone for 12 weeks. The 3 trials were restricted to patients with HCV genotype 1, which accounts for the majority of HCV infections, and they all had a primary endpoint of sustained virologic response (SVR) or undetectable viral load, assessed 12 weeks after discontinuation of the study drug.

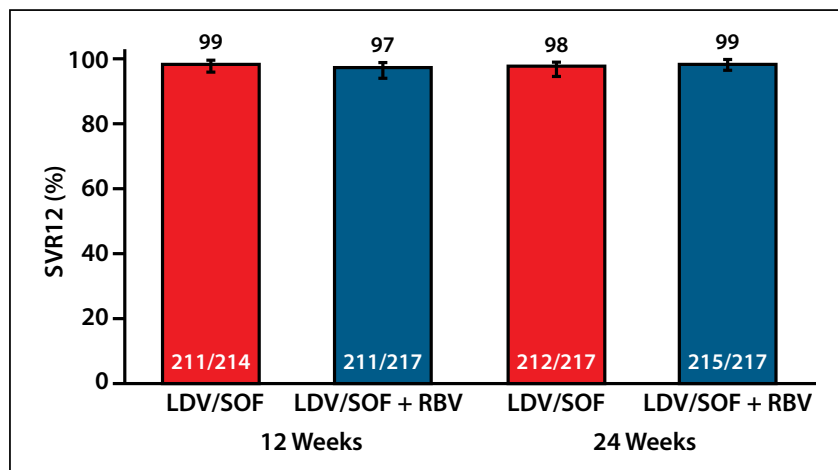


Figure 2. SVR12 rates in the ION-1 trial of sofosbuvir (SOF) plus ledipasvir (LDV), with or without ribavirin (RBV). ION-1, A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination [FDC] +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects With Chronic Genotype 1 HCV Infection. SVR12, sustained virologic response at week 12. Adapted from Mangia A et al. EASL abstract O164. *J Hepatol.* 2014;60(suppl 1):S253.³

ION-1: 12-Week Vs 24-Week Regimens in Treatment-Naive Patients

ION-1 enrolled 865 treatment-naive, genotype 1 HCV patients in the United States and Europe. Most patients (approximately 60%) were male, and the mean age was 52 years.^{3,4} Patients were randomized evenly across 4 treatment arms to receive the sofosbuvir/ledipasvir FDC pill with or without ribavirin for 12 weeks or 24 weeks. More than two-thirds of patients had HCV subtype 1a, and 16% had compensated liver cirrhosis. Patients were stratified for treatment based on these characteristics. Patient enrollment was not restricted based on upper age limit or body mass index, and no neutrophil minimum was required. All 4 treatment arms yielded cures in close to 100% of patients. SVR12 rates from patients receiving the ribavirin-containing regimen were equivalent after 12 weeks or 24 weeks

(97% vs 99%, respectively), and 12 or 24 weeks of treatment that excluded ribavirin yielded similar results (99% vs 98%, respectively; Figure 2). Of the 431 patients who received 12 weeks of treatment with or without ribavirin, 11 patients (2.5%) failed to achieve an SVR12. However, only 1 of these patients relapsed, and the remaining 10 patients were lost to follow-up. Patients with HCV subtypes 1a and 1b showed similar cure rates, and no significant differences were observed in SVR12 rates between patients with cirrhosis (94%-100%) vs those without cirrhosis (97%-99%). The most frequent AEs reported for sofosbuvir plus ledipasvir were mild and included headache (25%), fatigue (23%), and nausea (12%), and 32 patients (4%) had treatment-emergent severe AEs. In the absence of ribavirin, 0 patients who received 12 weeks of treatment and 2 patients who received 24 weeks of treatment discontinued treatment owing to an AE.

ION-2: 12-Week Vs 24-Week Regimens in Treatment-Experienced Patients

ION-2 had the same 4-arm study design as ION-1, but ION-2 enrolled 440 HCV patients who failed previous treatment consisting of pegylated interferon- α plus ribavirin with or without a protease inhibitor.^{5,6} Approximately 65% of patients were male, and the average age was 56 years. Twenty percent of patients had compensated cirrhosis, 79% had HCV genotype 1a infection, and 45% had never reached undetectable viral load from interferon-based treatment. Half of patients had failed prior treatment of a protease inhibitor combined with pegylated interferon- α plus ribavirin. All 4 treatment arms demonstrated high rates of SVR12. In patients who received sofosbuvir/ledipasvir plus ribavirin, SVR12 rates were 96% (95% CI, 91%-99%) with 12 weeks of treatment and 99% (95% CI, 95%-100%) with 24 weeks of treatment. In patients who did not receive ribavirin, SVR12 rates were 94% (95% CI, 87%-97%) with 12 weeks of treatment and 99% (95% CI, 95%-100%) with 24 weeks. Cure rates were similar for patients with HCV genotype 1a or 1b. Virtually all patients with cirrhosis achieved SVR12 after 24 weeks of treatment; however, cure rates were slightly lower at 12 weeks of treat-

ment with ribavirin (82%) or without (86%). At least half of the patients without a cure were lost to follow-up.

No new safety signals were raised by the treatment combinations. Nine patients (2%) receiving 24 weeks of treatment experienced serious AEs, but no treatment discontinuations owing to an AE were reported across the 4 arms. The most common AEs in the 4 arms were fatigue (21%-45%), headache (23%-32%), and nausea (6%-23%). As demonstrated in ION-1, neither the addition of ribavirin nor extension of treatment from 12 weeks to 24 weeks significantly improved SVR12 rates; moreover, the authors noted that extending standard treatment to 24 weeks would result in overtreatment in nearly all patients.

ION-3: 8-Week Vs 12-Week Regimens in Treatment-Naive Patients

Phase 2 data for an 8-week regimen of sofosbuvir and ledipasvir yielded high SVR12 rates regardless of previous treatment, prompting the investigation of 8 weeks vs 12 weeks of treatment in the ION-3 (Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination \pm Ribavirin for the Treatment of HCV [ION-3]) trial.^{7,8} ION-3 randomly assigned 647 treatment-naive, HCV genotype 1 patients without cir-

rhosis to receive 8 weeks of the sofosbuvir/ledipasvir FDC tablet with or without ribavirin or 12 weeks of sofosbuvir/ledipasvir alone. Patients were stratified by HCV genotype 1a vs 1b. Rates of SVR12 were 94% (95% CI, 90%-97%) for 8 weeks of sofosbuvir/ledipasvir, 93% (95% CI, 89%-96%) for 8 weeks of the same treatment plus ribavirin, and 95% (95% CI, 92%-98%) for 12 weeks of sofosbuvir/ledipasvir FDC treatment without ribavirin. The addition of ribavirin to the 8-week single-pill regimen did not improve the cure rate ($P=.70$), and the 8-week 2-drug FDC regimen was noninferior to the 12-week regimen ($P=.52$). No viral breakthroughs occurred. Relapses were observed in 11 patients (5%) who received only sofosbuvir/ledipasvir for 8 weeks, 9 patients (4%) who also received ribavirin for 8 weeks, and 3 patients (1%) in the 12-week, ribavirin-free treatment arm. Treatment was well tolerated overall. Patients treated with ribavirin experienced a higher frequency of AEs compared with the ribavirin-free treatment arms. No patients who received the 8-week regimen without ribavirin discontinued treatment owing to an AE.

To characterize the benefit of treatment with ribavirin vs without it, the quality of life of patients in ION-1 was investigated.⁹ Patients receiving the 12-week treatment regimen ($n=431$)

ABSTRACT SUMMARY Sofosbuvir Plus Ribavirin, an Interferon-Free Regimen, in the Treatment of Treatment-Naive and Treatment-Experienced Patients With Chronic Genotype 4 HCV Infection

HCV genotype 4 is the most common genotype in Egypt and other areas of the Middle East. A randomized, open-label, phase 2 study was conducted in 60 patients of Egyptian ancestry living in the United States to determine the safety and efficacy of sofosbuvir plus ribavirin in this patient population (Abstract P1243). Treatment-naive and treatment-experienced patients were enrolled, including approximately 20% with compensated cirrhosis. Patients were stratified based on prior treatment

and presence or absence of cirrhosis and were then randomized to receive 12 or 24 weeks of sofosbuvir (400 mg daily) plus ribavirin. Patients had a mean age of 54 years (range, 26-75 years). Approximately half had received prior treatment, and approximately one-third of patients in each arm were null responders. Treatment-naive patients exhibited SVR12 rates of 79% and 100% for 12 or 24 weeks of treatment, respectively. Viral clearance rates were lower overall for previously treated patients, with SVR12

rates of 59% and 87% for 12 vs 24 weeks of treatment. Therefore, the longer treatment duration was of benefit for both treatment-naive and treatment-experienced patients with HCV genotype 4. All virologic failures were from relapse, with the exception of 1 patient with viral breakthrough at treatment week 10. Serious AEs were observed in 3 patients (10%) randomized to 24 weeks of treatment, and no patients discontinued study treatment because of an AE. A similar study in Egypt is ongoing.

completed questionnaires (including the Short Form-36, the Functional Assessment of Chronic Illness Therapy-Fatigue, the Chronic Liver Disease Questionnaire-HCV, and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem) at baseline, during, and after treatment. Ribavirin-free treatment was numerically superior for mental, physical, and total health-related quality of life and was significantly superior in terms of fatigue ($P=.0006$), total well-being ($P=.053$), work productivity ($P<.0001$), and nonwork activities ($P=.0017$). Because the recent phase 3 studies show that ribavirin can be eliminated without compromising treatment efficacy, many

of the potential quality-of-life issues have been eliminated. Nonetheless, the study clearly demonstrates the favorable patient-reported outcomes for the combined single-pill treatment over treatment with ribavirin.

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PEARL-III: 12 Weeks of ABT-450/R/267 + ABT-333 Achieved SVR in >99% of 419 Treatment-Naïve HCV Genotype 1B-Infected Adults With or Without Ribavirin

The phase 3 PEARL-III (A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 [ABT-450/R/ABT-267] and ABT-333 With and Without Ribavirin [RBV] in Treatment-Naïve Adults With Genotype 1B Chronic Hepatitis C Virus [HCV] Infection) study was designed to test outcomes after 12 weeks of treatment with the 3D regimen with or without ribavirin in treatment-naïve, noncirrhotic patients with HCV genotype 1b.¹ The trial enrolled 419 patients in the United States, Europe, and Russia, with a mean age of 49 years. Approximately 45% of patients were male, and 21% of patients had the *IL28B* CC genotype. The mean HCV RNA level was 6.3 log₁₀ IU/mL. Approximately 30% of patients had a Metavir fibrosis score of F2 or F3. Similarly high rates of SVR12 were observed with or without ribavirin (99.5% [95% CI, 98.6%-100.0%] vs 99.0% [95% CI, 97.7%-100.0%], respectively). The data demonstrated

both noninferiority and superiority to the historic rate with telaprevir-based treatment in a similar patient population. One patient in the ribavirin arm experienced a virologic rebound during treatment. The 2 patients in the ribavirin-free arm who did not achieve SVR12 completed the study treatment but did not complete follow-up testing at posttreatment week 12. AEs of any grade were more frequent in patients receiving ribavirin (80.0% vs 67.0%; $P=.003$) and included headache (11.9% vs 5.3%; $P=.02$), nausea (11.0% vs 4.3%; $P=.02$), and insomnia (9.0% vs 3.3%; $P=.02$). In keeping with previous reports, decreased hemoglobin levels ($P<.001$) and abnormally high bilirubin levels ($P=.003$) were observed more frequently in the ribavirin-containing arm. Serious AEs were observed in 4 patients (1.9%) in each arm.

Final results from the open-label, nonrandomized, phase 2 PEARL-I (A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Coadministration of ABT-450 With

Ritonavir [ABT-450/R] and ABT-267 in Adults With Chronic Hepatitis C Virus Infection) trial were available for the 2 arms of treatment-naïve patients, with interim data from treatment-experienced patients also available.² Treatment-naïve, noncirrhotic patients with HCV genotype 4 received 12 weeks of treatment with daily ABT-405 (150 mg) and ritonavir (100 mg) plus daily ombitasvir either with ribavirin ($n=42$) or without it ($n=44$; 1000-1200 mg daily). At the end of treatment, 100.0% of patients treated with ribavirin and 95.5% of patients treated without ribavirin had undetectable levels of HCV. The SVR12 rates were 100.0% in patients who received ribavirin vs 90.9% in those who did not. Among the 4 patients who failed to respond in the ribavirin-free arm, 1 (2.3%) experienced viral breakthrough, 2 (4.6%) relapsed, and 1 (2.3%) was lost to follow-up. The third arm enrolled 49 noncirrhotic, treatment-experienced patients who received the ribavirin-containing treatment for 12 weeks.

ABSTRACT SUMMARY Once-Daily Simeprevir (TMC435) With Peginterferon/Ribavirin in Treatment-Naïve or Treatment-Experienced Chronic HCV Genotype 4-Infected Patients: Final Results of a Phase III Trial

The open-label, multicenter, single-arm, phase 3 RESTORE (An Open-Label, Single-Arm Phase III Study to Evaluate the Efficacy, Safety and Tolerability of TMC435 in Combination With PegIFN Alfa-2a [Pegasys] and Ribavirin [Copegus] in Treatment-Naïve or Treatment-Experienced, Chronic Hepatitis C Virus Genotype-4 Infected Subjects) trial evaluated the safety and efficacy of the investigational HCV NS3/4A protease inhibitor simeprevir in combination with pegylated interferon- α and ribavirin in patients with chronic HCV genotype 4 infection and compensated liver

disease (Abstract 1319). Patients had a median age of 49 years, 7.5% had *IL-28B* CC genotype, and Metavir fibrosis stages F3 or F4 were observed in 14% and 29% of patients, respectively. All patients received simeprevir (150 mg daily) during weeks 1 to 12. All patients also received pegylated interferon- α (180 μ g weekly) and ribavirin based on weight (1000-1200 mg daily) during weeks 1 to 24. For previously untreated patients and prior relapsers, treatment was halted after 24 weeks if they met the response-guided therapy criteria of undetectable HCV RNA at treatment

week 12. Patients with detectable HCV RNA at treatment week 12, as well as all prior null or partial responders, received the interferon/ribavirin regimen until treatment week 48. By week 24, treatment was completed in 88.6% of treatment-naïve patients and 90.9% of prior relapsers. SVR12 rates were 65.4% (70 of 107 patients) for the entire study population, 82.9% (29 of 35 patients) for treatment-naïve patients, 86.4% (19 of 22 patients) for prior relapsers, 60.0% (6 of 10 patients) for prior partial responders, and 40.0% (16 of 40 patients) for prior null responders.

At the end of treatment, 100.0% of previously treated patients showed no evidence of HCV RNA. The SVR12 rate, available for 37 patients, was also 100%. Patients in the ribavirin-free arm experienced the fewest AEs (77% vs 86%-88%). One serious AE occurred in the ribavirin-free arm and was unrelated to study treatment. One patient (2.3%) in the ribavirin-free

arm experienced aspartate aminotransferase elevation greater than 5 times the upper limit of normal, which resolved with continuing study treatment, and 3 treatment-experienced patients (6.1%) showed transient total bilirubin levels greater than 3 times the upper limit of normal. A decrease in hemoglobin level below 10 g/dL occurred in 1 patient in each arm.

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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

One of the most common indications for liver transplantation worldwide is liver disease resulting from chronic HCV infection.¹ HCV patients with liver transplantation universally experience reinfection, with 20% to 30% of transplant recipients exhibiting graft cirrhosis within 5 years. Subsequent graft loss is a common occurrence, underscoring the urgent need for improved HCV treatment options

in this patient population.² Current therapy, which is based on combinations with interferon and ribavirin, is associated with treatment-limiting toxicities, including severe anemia, other cytopenias, and graft rejection. Given the many drugs required in the transplant setting, studies must investigate potential drug interactions as well as efficacy.

Dr Paul Kwo presented preliminary results of the open-label phase 2

M12-999 study, an ongoing trial designed to evaluate the safety and efficacy of the same drug combination investigated in the SAPPHERE-I and SAPPHERE-II trials.³ The 34 patients in the phase 2 study were noncirrhotic liver transplant recipients with recurrent HCV genotype 1 infection. The combination consisted of oral, once-daily administration of ABT-450 (150 mg), ritonavir (100 mg), and ombitasvir

(25 mg), plus dasabuvir (250 mg twice daily) and ribavirin, which was dosed at the investigator's discretion. The study's primary endpoint was SVR12.

Among the patients enrolled, the time since transplantation was a mean 47.9 months, and 79.4% were male. The mean age was 59.6 years, and the mean body mass index (BMI) was 29.7 kg/m². Stage F2 fibrosis was reported in 47% of patients; 76.5% of patients had the *IL28B* non-CC genotype, and 85.3% of patients had HCV subtype 1a disease. All patients were taking immunosuppressive medications consisting of tacrolimus (85.3%) or cyclosporine (14.7%). In a phase 1 drug interaction study, addition of the 3D regimen to a calcineurin inhibitor increased half-life by 7-fold for tacrolimus and 3-fold for cyclosporine. Therefore, dosing requirements for these drugs were reduced accordingly in the M12-999 trial. Patients received the 3D regimen plus

ribavirin dosed at the treating physician's discretion for 24 weeks. Preliminary results showed efficacy in 100% of patients, consisting of 100% rapid viral response after 4 weeks of treatment and 100% end-of-treatment response. A preliminary analysis of 26 patients showed an SVR12 rate of 96.2%. No viral breakthrough was observed. One patient relapsed on day 3 following treatment. At the time of relapse, this patient had resistance-associated variants that were not present at baseline.

The treatment was generally well tolerated, and most AEs were mild. No deaths or episodes of acute or chronic rejection were observed. The most common AEs of any grade occurring in at least 25% of patients were headache (44.1%), fatigue (41.2%), cough (29.4%), and insomnia (26.5%). Two patients had serious AEs: 1 patient had hypotension and tachycardia associated with initiation of tamsulosin after

elective surgery, and 1 diabetic patient with a history of peripheral edema had moderate peripheral edema and pain in the extremities. One patient discontinued study drug treatment after week 18 owing to AEs that included moderate rash, memory impairment, and anxiety; however, this patient achieved an SVR12. Laboratory abnormalities of interest included 2 patients (5.9%) with total bilirubin exceeding 3 times the upper limit of normal.

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Sofosbuvir and Ribavirin for the Treatment of Chronic HCV With Cirrhosis and Portal Hypertension With and Without Decompensation: Early Virologic Response and Safety

The prevalence of end-stage liver disease resulting from HCV infection is increasing worldwide. However, there are no approved treatments for these very ill patients, who cannot tolerate the harsh AEs associated with interferon. Patients with compensated cirrhosis who achieve an SVR have a significantly lower risk of hepatic decompensation and death. A trial was therefore designed to investigate the effect of viral suppression on clinical outcomes in patients with cirrhosis and portal hypertension, with or without hepatic decompensation. Eligible patients had compensated cirrhosis (CTP score 5-6; class A) or decompensated cirrhosis (CTP score 7-9; class B) with esophageal or gastric varices and a hepatic venous pressure gradient exceeding 6 mmHg. The trial's primary objective was SVR12. Patients

in arm 1 (n=25) received sofosbuvir (400 mg) plus ribavirin (1000-1200 mg) for 48 weeks. Patients in arm 2 (n=25) were observed for the first 24 weeks and then received 48 weeks of the 2-drug combination.

Dr Nezam Afdhal presented preliminary results based on the first 24 weeks of the study. Approximately three-fourths of patients were male, and the median age was approximately 56 years.¹ Approximately 40% had HCV genotype 1a, and 30% had 1b. Approximately 80% had received prior treatment for HCV infection. Approximately 60% of patients were classified as CTP class B and the remainder as class A, except for 1 class C patient. Patients had a mean hepatic venous pressure gradient of 16.5 mmHg at baseline. Twenty-two patients, all in arm 1, completed 24

weeks of treatment. Three patients in arm 1 and 4 patients in arm 2 discontinued treatment or observation. By week 4, 100% of patients with a CTP class A score and 75% of patients with a CTP class B score had undetectable HCV RNA, reflecting an overall rapid response that was fastest in patients with compensated cirrhosis (Figure 3). By week 24, 93% of CTP B patients had undetectable viral RNA, and the CTP A patients continued to show no detectable viral RNA. No viral breakthroughs were observed during treatment. Although these results are promising, longer observation of the treated patients is required to determine whether this treatment can produce long-term cures.

During the 24-week period of treatment or observation, several laboratory parameters improved with treat-

ment. Platelet counts and albumin levels improved in the sofosbuvir-plus-ribavirin arm but not in the observation arm). As seen previously in patients receiving ribavirin, bilirubin levels rose and hemoglobin levels fell in the treated patients while remaining stable in patients under observation. Alanine aminotransferase levels normalized in most patients, falling by an average of 72 U/L in arm 1 and increasing slightly in arm 2. The Model for End-Stage Liver Disease (MELD) score declined for 2 of 9 treated CTP class A patients and for 11 of 16 treated CTP class B patients. For patients in the observation arm, MELD scores decreased in 4 of 11 CTP class A patients and 6 of 13 CTP class B patients. Clinical events showed a greater improvement with treatment compared with observation; in arm 1, the number of patients with ascites fell from 6 to 0, as compared with a reduction from 9 to 7 in arm 2. The number of patients with hepatic encephalopathy also declined in the treatment arm (5 at baseline vs none at 24 weeks) but not in the observation arm (2 at baseline vs 4 at 24 weeks).

AEs were observed in 16 patients (84%) in the treatment arm and 14 patients (56%) in the observation arm. Grade 3/4 AEs were observed in 3 patients in arm 1 vs 2 patients in arm 2. Serious AEs were observed in 3 patients

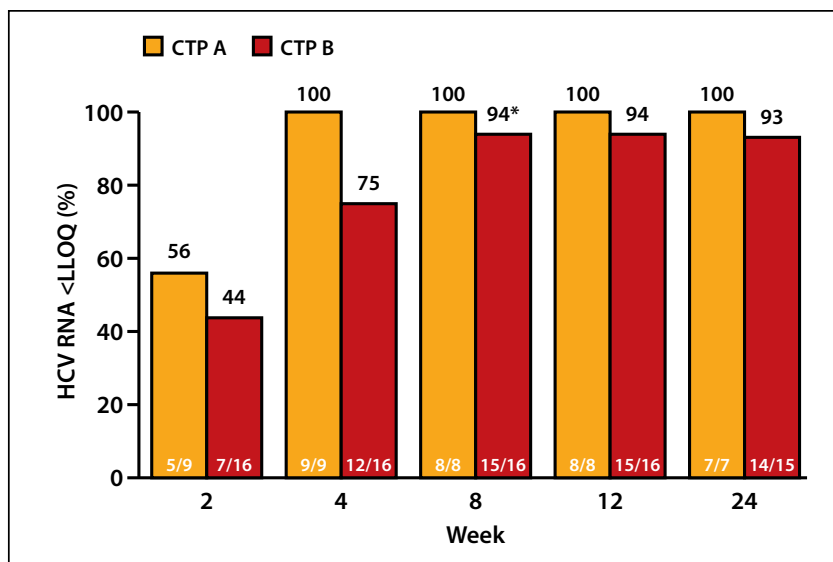


Figure 3. Preliminary results from a trial investigating the effect of viral suppression on clinical outcomes in patients with cirrhosis and portal hypertension, with or without hepatic decompensation. *One patient was a nonresponder at week 8. CTP, Child-Turcotte-Pugh; HCV, hepatitis C virus; LLOQ, lower limit of quantification. Adapted from Afdhal N et al. EASL abstract O68. *J Hepatol.* 2014;60(suppl 1):S28.¹

in arm 1 vs 4 patients in arm 2. The most common AEs of any grade in the treatment arm were nausea (32%), asthenia (24%), and pruritus (24%). One patient in the treatment arm discontinued therapy owing to an AE, and 2 patients in the observation arm discontinued owing to disease progression. Dr Afdhal underscored the importance of reporting additional safety findings as soon as possible owing to the lack of treatment

options for this patient population. He suggested, however, that the combination of sofosbuvir plus ledipasvir may be a potential treatment option that lacks the adverse effects associated with ribavirin.

Reference

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ABSTRACT SUMMARY 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

The randomized, open-label, phase 2a COSMOS trial investigated the efficacy and safety of sofosbuvir (400 mg daily) and simeprevir (150 mg daily) with or without ribavirin (1000–1200 mg daily in 2 doses) in treatment-naïve or treatment-experienced patients with chronic HCV genotype 1 (Abstract O7). Patients were divided into 2 cohorts: prior null responders with a METAVIR score of F0 to F2 (cohort 1; n=80) and treatment-

naïve patients and prior null responders with a Metavir score of F3 to F4 (cohort 2; n=87). Dr Mark Sulkowski presented findings from cohort 1. Patients received study drugs with or without ribavirin for 12 or 24 weeks. For the 2 groups of patients treated for 12 weeks, sofosbuvir plus simeprevir yielded an SVR12 rate of 93% (13 of 14 patients), and the addition of ribavirin yielded an SVR12 rate of 96% (26 of 27 patients). For the 2 arms

of patients treated for 24 weeks, SVR12 rates were 93% (14 of 15 patients) without ribavirin and 79% (19 of 24 patients) with ribavirin. All patients with HCV genotype 1b and all patients with HCV genotype 1a without the Q80K mutation achieved SVR12. However, in patients with genotype 1a infection and the Q80K mutation, SVR12 rates were 83% to 89% after 12 weeks of treatment and 89% to 100% after 24 weeks of treatment.

All-Oral Dual Therapy With Daclatasvir and Asunaprevir in Patients With HCV Genotype 1B Infection: Phase 3 Study Results

The double-blind, placebo-controlled, multicenter, randomized phase 3 HALLMARK-DUAL (A Phase 3 Study With Asunaprevir and Daclatasvir [DUAL] for Null or Partial Responders to Peginterferon Alfa and Ribavirin [P/R], Intolerant or Ineligible to P/R Subjects and Treatment-Naive Subjects With Chronic Hepatitis C Genotype 1b Infection) trial examined the safety and efficacy of daclatasvir (60 mg daily) plus asunaprevir (100 mg twice daily) in patients with HCV genotype 1b with or without cirrhosis. Patients were enrolled regardless of whether they had received prior treatment. Treatment-naive patients (n=305) were randomized 2:1 to receive the all-oral study drugs for 24 weeks or matched placebo for 12 weeks, followed by entry into another study of the same drugs. There were 203 patients who achieved a prior partial response or null response to pegylated interferon- α plus ribavirin, and 235 patients who were ineligible for or intolerant of the same treatment. Dr Michael Manns presented results from the trial.¹ SVR12 rates were 90% (182 of 203 patients) for treatment-naive patients, 82% (98 of 119 patients) for prior null responders, 81% (68 of 84 patients) for prior partial responders, and 82% (192 of 235 patients) for patients

who were ineligible for or intolerant of interferon. For the 77 patients with advanced fibrosis and/or cirrhosis with thrombocytopenia, the SVR12 rate was 73%. Viral breakthrough was observed in 9 treatment-naive patients (4%), 26 prior nonresponders (13%), and 20 patients (9%) who were ineligible for or intolerant of interferon/ribavirin. Serious AEs occurred in 6% of treatment-naive patients, 5% of nonresponders, and 7% of interferon ineligible/intolerant patients. AEs leading to discontinuation occurred in 3% of treatment-naive patients, 1% of nonresponders, and 1% of interferon ineligible/intolerant patients.

Dr Jia-Horng Kao and colleagues presented late-breaking results in cirrhotic patients (n=206) vs noncirrhotic patients (n=437) from the HALLMARK-DUAL study.² Baseline characteristics were similar between these groups, and approximately 90% of patients completed study treatment. SVR12 rates were 84% in the cirrhotic patients and 85% in the noncirrhotic patients. Subgroup analysis showed that SVR12 rates were similar for cirrhotic vs noncirrhotic patients who were treatment-naive (91% for both) and for patients who were ineligible or intolerant of interferon/ribavirin treatment (81% vs 84%, respectively). Unexpectedly,

outcomes were superior for cirrhotic vs noncirrhotic patients who were prior nonresponders (87% vs 80%), prior null responders (88% vs 80%), and prior partial responders (86% vs 79%). Similar proportions of cirrhotic and noncirrhotic patients failed to achieve SVR12 (17% vs 15%, respectively), with on-treatment failures owing to virologic breakthrough in 8% vs 9% of patients, respectively, and detectable or missing RNA in 4% vs 2% of patients, respectively. The oral drug combination was generally well tolerated. AEs of any grade occurred at similar frequencies in both groups, with the most common AE being headache (25% in both groups). No clinically meaningful differences emerged in cirrhotic vs noncirrhotic patients based on frequencies of serious AEs, discontinuations owing to an AE, or grade 3/4 transaminase elevations. No deaths occurred.

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ABSTRACT SUMMARY Retreatment of Sofosbuvir + Ribavirin Failure With Sofosbuvir-Containing Regimens in Patients With Genotype 2 or 3

Optimal treatment for HCV patients who have failed previous therapy is unknown. This open-label study enrolled HCV genotype 2 and 3 patients who failed to achieve an SVR with sofosbuvir-containing regimens (Abstract O8). The 107 patients received treatment with either sofosbuvir, ribavirin, and peginterferon for 12 weeks or sofosbuvir and ribavirin for 24 weeks. The mean patient age in

both treatment groups was 53 years. There were more men than women in both groups (86% in the sofosbuvir/ribavirin arm and 77% in the sofosbuvir/ribavirin/peginterferon arm). Compensated cirrhosis was present in 41% of patients receiving sofosbuvir, ribavirin, and peginterferon and in 34% of patients receiving sofosbuvir and ribavirin. Data were presented for 6 patients with geno-

type 2 and 60 patients with genotype 3. SVR12 rates were 92% for patients in the sofosbuvir/ribavirin/peginterferon arm and 63% in the sofosbuvir/ribavirin arm. Treatment with sofosbuvir, ribavirin, and peginterferon was associated with a higher SVR12 rate in both genotypes (genotype 2, 100% [vs 50% with sofosbuvir/ribavirin]; genotype 3, 91% [vs 63% with sofosbuvir/ribavirin]).

Sofosbuvir/Ledipasvir Fixed Dose Combination Is Safe and Effective in Difficult-to-Treat Populations Including Genotype-3 Patients, Decompensated Genotype-1 Patients, and Genotype-1 Patients With Prior Sofosbuvir Treatment Experience

The sofosbuvir/ledipasvir FDC treatment regimen, in courses of 8 to 24 weeks, has been studied in phase 3 studies of HCV genotype 1 patients, including those with compensated cirrhosis. However, some HCV populations continue to show poor tolerability or efficacy with current regimens. In response to the need for improved treatments for these patient subtypes, the open-label, phase 2 ELECTRON-2 study examined 12 weeks of the 2-drug combination with or without ribavirin in difficult-to-treat patients.¹ Patients with HCV genotype 1 who had relapsed following prior exposure to sofosbuvir (n=19) received the 2-drug FDC tablet plus ribavirin (arm 1). Patients with HCV genotype 1 and CTP class B cirrhosis (n=20) received the FDC tablet without ribavirin (arm 2), as ribavirin toxicity is often problematic in this patient population. Patients with treatment-naïve HCV genotype 3 (n=51) were randomized 1:1 to receive the FDC tablet without ribavirin (arm 3) or with ribavirin (arm 4). The ribavirin dosage was based on weight and ranged from 1000 mg to 1200 mg daily. The trial's primary efficacy endpoint was SVR12.

Across the 4 arms, median age was 43 to 56 years (range, 22-72 years), and the proportion of males ranged from 42% to 85%. Median BMI ranged from 27 kg/m² to 31 kg/m². In arms 1 to 4, the proportion of patients with cirrhosis was 0%, 100%, 12%, and 19%, respectively, and the proportion of patients with the *IL28B* CC genotype was 21%, 35%, 36%, and 58%. Mean HCV RNA ranged from 6.0 log₁₀ IU/mL to 6.3 log₁₀ IU/mL (range, 4.0-7.6 log₁₀ IU/mL). Prior treatments for patients in arm 1 included 12 weeks of sofosbuvir plus ribavirin (n=10), 6 weeks of sofosbuvir and ledipasvir plus ribavirin (n=8), and sofosbuvir plus GS-9669 and ribavirin

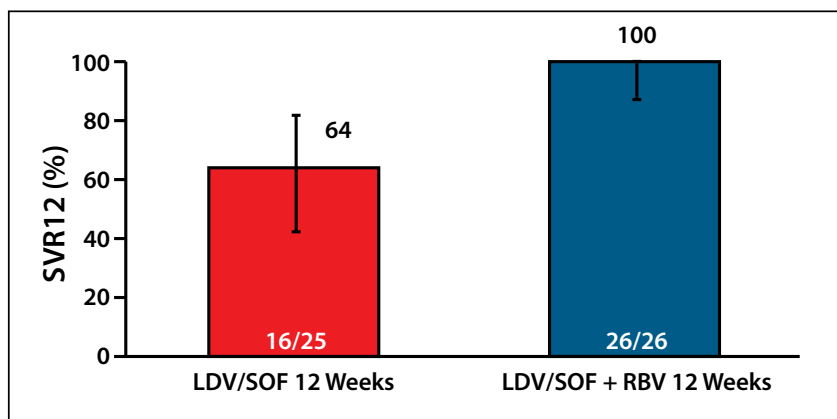


Figure 4. Results from the ELECTRON-2 trial of sofosbuvir (SOF) plus ledipasvir (LDV), with or without ribavirin (RBV). Error bars represent 95% CI. ELECTRON-2, Sofosbuvir/Ledipasvir Fixed Dose Combination Is Safe and Effective in Difficult-to-Treat Populations Including Genotype-3 Patients, Decompensated Genotype-1 Patients, and Genotype-1 Patients With Prior Sofosbuvir Treatment Experience; SVR12, sustained virologic response at week 12. Adapted from Gane EJ et al. EASL abstract O16. *J Hepatol.* 2014;60(suppl 1):S8.¹

(n=1). All of these patients demonstrated SVR12 in the current study.

Clinical and laboratory data for the patients in arm 2 reflected a population with fairly advanced disease, with a median bilirubin of 1.5 mg/dL (range, 0.7-3.7 mg/dL), a median serum albumin of 3.1 g/dL (range, 2.3-3.8 g/dL), and a median international normalized ratio of 1.2 (range, 1.0-3.0). The median platelet count was 84,000 cells/mm³ (range, 44,000-162,000 cells/mm³), 20% of patients had ascites, and 30% had hepatic encephalopathy. Following 12 weeks of study treatment, 13 of 20 patients (65%) demonstrated SVR12 and 7 patients (35%) relapsed. Given the lack of safe and effective treatments for patients with decompensated cirrhosis, this outcome represents a promising option. Patients with HCV genotype 3 benefited from the addition of ribavirin to sofosbuvir/ledipasvir, as the SVR12 rates for arms 3 and 4 were 64% and 100%, respectively (Figure 4).

The study treatment regimens were safe and generally well tolerated. In both arms, most patients experienced an AE. Grade 3/4 AEs were reported in 1 patient (5%) in arm 2 and 3 patients (12%) in arm 3, with serious AEs observed in 2 patients (10%) in arm 2 and 4 patients (16%) in arm 4. One patient in arm 3 (4%) discontinued treatment owing to perforated sigmoid diverticulitis on study day 7 without achieving a cure. The most common AEs of any grade across the 4 arms were headache (range, 20%-40%), upper respiratory tract infection (range, 21%-40%), and nausea (range, 15%-36%). Grade 3/4 laboratory abnormalities were observed in 11%, 15%, 4%, and 27% of patients in arms 1, 2, 3, and 4, respectively.

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Sofosbuvir and Ribavirin for the Treatment of Recurrent Hepatitis C Infection After Liver Transplantation: Results of a Prospective, Multicenter Study

A single-arm trial investigated the combination of sofosbuvir (400 mg) plus ribavirin (400-1200 mg) in 40 patients with HCV of any genotype who had undergone liver transplantation between 6 months and 150 months before enrollment in the study.¹ Key inclusion requirements included a CTP score of no greater than 7, a MELD score of no greater than 17, and absence of organ rejection. Both treatment-naïve and treatment-experienced patients were enrolled. Patients with current signs of decompensation were excluded, as were those taking corticosteroids at high dosages (>5 mg/day of prednisone). In addition to sofosbuvir (400 mg daily), the study regimen included ascending-dose ribavirin starting at 400 mg daily, with escalation up to 1200 mg daily based on adequate hemoglobin levels. Treatment lasted 24 weeks, with follow-up at 12 and 24 weeks posttreatment to assess SVR.

Patients' median age was 59 years (range, 49-75 years), and 78% were male. Seventy-five percent of patients had a BMI of less than 30 kg/m², and the median HCV RNA level was 6.6 log₁₀ IU/mL (range, 4.5-7.6 log₁₀ IU/mL). HCV genotypes 1a, 1b, and 3 accounted for 55%, 28%, and 15% of patients, respectively, and 33% of patients had *IL28B* CC genotype. The median time since liver transplantation was 4.3 years (range, 1.0-10.6 years). By treatment week 4, 100% of patients had HCV RNA below the lower limit of quantification, which was sustained through treatment week 12. After cessation of treatment, 70% of patients achieved SVR12, and the same proportion achieved SVR24. The rates of HCV RNA decline were similar in responding patients (n=28) and those who relapsed (n=12), and did not appear to influence outcome. The mean total drug exposure for sofosbuvir, GS-331007, and ribavirin was also similar in patients who attained

SVR12 and those who relapsed. Mean exposure to ribavirin did not correlate with outcome.

The drug combination was generally well tolerated. Six patients (15%) experienced serious AEs, and 2 patients (5%) had AEs that led to discontinuation of study treatment. The most common AEs of any grade were fatigue (30%), diarrhea (28%), and headache (25%). Fifty-six percent of patients experienced a laboratory abnormality of grade 3/4, and the abnormalities were considered reflective of the posttransplant population. No deaths, graft losses, or episodes of graft rejection were reported, and no interactions between sofosbuvir and any immunosuppressive agents were observed.

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Commentary

Steven L. Flamm, MD

The European Association for the Study of the Liver (EASL) 2014 International Liver Congress was an extremely important meeting in regards to management of chronic hepatitis C virus (HCV) infection. Mature data were presented about the new direct-acting antiviral agents. Studies were presented on the optimum length of antiviral therapy and how to match patients with the best therapeutic regimen to optimize chances of attaining a sustained response. As data accumulate regarding the best use of novel medications, and more is learned about adverse events, trial enrollment has expanded to include so-called special populations, such as patients with decompensated

liver disease and those who have failed previous treatment.

The ION Trials

Preliminary data on ledipasvir and sofosbuvir in a fixed-dose combination regimen have been reported previously.^{1,2} The maturing data are now providing details about this regimen, including treatment duration and best use in specific populations. The ION-1 (A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination [FDC] +/- Ribavirin for 12 and 24 Weeks in Treatment-Naïve Subjects With Chronic Genotype 1 HCV Infection) trial evaluated the use of sofosbuvir and ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-naïve HCV genotype 1 patients.^{3,4} Sixteen

percent of the patients had compensated liver cirrhosis. The study showed that this combination was highly efficacious and very well tolerated. Treatment for 24 weeks was not superior to treatment for 12 weeks, and ribavirin did not improve outcomes.

The ION-3 (Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV [ION-3]) trial aimed to determine whether the treatment course of ledipasvir and sofosbuvir could be shortened to 8 weeks from the 12 weeks identified as optimal in ION-1.^{5,6} The trial enrolled treatment-naïve HCV genotype 1 patients without cirrhosis. The treatment arms consisted of ledipasvir and sofosbuvir, with and without ribavirin, given for 8 weeks; and a 12-week course of ledipasvir and sofosbuvir without ribavirin. The study found that the 8-week

course of sofosbuvir and ledipasvir had comparable sustained response rates to the 12-week course and, furthermore, that ribavirin was unnecessary. Results from ION-1 and ION-3 indicate that for noncirrhotic patients, an 8-week course of the fixed-dose regimen may suffice.

The ION-2 (Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV) trial enrolled previously treated HCV genotype 1 patients.^{7,8} As in ION-1, patients received treatment with sofosbuvir and ledipasvir, with or without ribavirin, for either 12 weeks or 24 weeks. Again, this study appeared to show that ribavirin was unnecessary. Both treatment durations were highly efficacious. The 24-week regimen appeared to be beneficial for patients with cirrhosis. With 12-week treatment, sustained virologic response (SVR) rates were 86% with sofosbuvir/ledipasvir alone vs 82% with sofosbuvir/ledipasvir plus ribavirin. In contrast, all cirrhotic patients treated for 24 weeks achieved SVR, regardless of whether ribavirin was used. The sofosbuvir and ledipasvir fixed-dose combination pill is expected to be approved by the US Food and Drug Administration (FDA) in late 2014.

The SAPPHERE Trials

The SAPPHERE trials evaluated a regimen consisting of ABT-450 boosted by ritonavir, a protease inhibitor; the NS5A inhibitor ombitasvir; the polymerase inhibitor dasabuvir; and ribavirin. In SAPPHERE-1 (A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 [ABT-450/R/ABT-267] and ABT-333 Co-Administered With Ribavirin [RBV] in Treatment-Naïve Adults With Genotype 1 Chronic Hepatitis C Virus [HCV] Infection), this regimen was administered for 12 weeks to HCV genotype 1 treatment-naïve patients without cirrhosis.⁹ A sustained response rate of 96% was observed. Similar results were found in SAPPHERE-2 (A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-

267 [ABT-450/R/ABT-267] and ABT-333 Co-Administered With Ribavirin [RBV] in Treatment-Experienced Adults With Genotype 1 Chronic Hepatitis C Virus [HCV] Infection), which enrolled previously treated patients without cirrhosis.¹⁰ FDA approval for this regimen is expected in late 2014.

TURQUOISE-2

The same regimen was evaluated in TURQUOISE-II (A Study to Evaluate the Safety and Effect of ABT-450, Ritonavir and ABT-267 [ABT-450/R/ABT-267] and ABT-333 Coadministered With Ribavirin [RBV] in Hepatitis C Virus [HCV] Genotype 1-Infected Adults With Compensated Cirrhosis), the first such trial dedicated specifically to HCV patients with cirrhosis.^{11,12} This large trial of 380 patients administered treatment for 12 weeks and 24 weeks. The sustained response rate was 92% with the 12-week course and 96% with the longer course. The 12-week course was associated with a disadvantage in one patient subgroup: treatment-naïve and treatment-experienced genotype 1a patients who failed to respond to previous treatment. Among these patients, the sustained response rate was 80% with the 12-week course and 93% in the 24-week course. The 12-week course sufficed for all other patient subgroups.

The PEARL Studies

The PEARL studies evaluated whether ribavirin could be eliminated from a direct-acting antiviral regimen combining ABT-267 (ombitasvir) and ABT-333 (dasabuvir).¹³ PEARL-III (A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 [ABT-450/R/ABT-267] and ABT-333 With and Without Ribavirin [RBV] in Treatment-Naïve Adults With Genotype 1b Chronic Hepatitis C Virus [HCV] Infection) enrolled noncirrhotic HCV genotype 1b patients, who received the regimen with or without ribavirin for 12 weeks.¹⁴ In general, HCV genotype 1b is more responsive to treatment than other genotypes. In PEARL-III, the SVR

rates were 99.5% with ribavirin and 99% without ribavirin, suggesting that ribavirin is not needed with this regimen. PEARL-IV (A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 [ABT-450/R/ABT-267] and ABT-333 With and Without Ribavirin [RBV] in Treatment-Naïve Adults With Genotype 1a Chronic Hepatitis C Virus [HCV] Infection [PEARL-IV]), presented at the 2014 Digestive Disease Week, used the same treatment protocol in HCV genotype 1a patients, and it found that ribavirin was beneficial.^{15,16} The SVR rate was 97% with ribavirin and 90% without ribavirin, suggesting that ribavirin is necessary for HCV genotype 1a patients.

Special Patient Populations

In HCV, special populations are those patients who had a poor response or who required special considerations with interferon- α -based regimens. Two studies presented at EASL focused on HCV genotype 4 patients. Although genotype 4 is rare in the United States, it is common in other parts of the world, particularly Egypt. A study of HCV genotype 4 patients (treatment-naïve or treatment-experienced) of Egyptian ancestry living in the United States evaluated the safety and efficacy of sofosbuvir plus ribavirin.¹⁷ Among treatment-naïve patients, SVR12 rates were 79% for 12 weeks of treatment and 100% for 24 weeks of treatment. Previously treated patients had lower response rates; SVR rates were 59% for the 12-week regimen and 87% for the 24-week regimen. PEARL-1 (A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Coadministration of ABT-450 With Ritonavir [ABT-450/R] and ABT-267 in Adults With Chronic Hepatitis C Virus Infection) enrolled treatment-naïve, noncirrhotic HCV genotype 4 patients in a trial evaluating ABT-450 and ritonavir plus daily ombitasvir either with or without ribavirin. The SVR12 rates were 100% with ribavirin vs 91% without ribavirin.¹⁸ More research is needed for genotype 4 patients.

Another important patient population is those who fail therapy with the

newer agents. Although novel approaches, and even current approaches, are more effective than previous treatments, there are still some patients who do not respond to therapy. The best way to manage these patients is unknown. The ELECTRON-2 (All-Oral Sofosbuvir-Based 12-Week Regimens for the Treatment of Chronic HCV GT 1 Infection) trial examined the sofosbuvir/ledipasvir fixed-dose combination in several difficult-to-treat populations, including 19 genotype 1 patients who had received previous treatment with sofosbuvir.¹⁹ All of these patients achieved an SVR with this regimen. This outcome is encouraging, even with the small number of patients.

A study by Esteban and colleagues included patients with HCV genotype 2 and 3 who had failed previous treatment with sofosbuvir.²⁰ The patients received sofosbuvir plus ribavirin for 24 weeks or sofosbuvir, peginterferon, and ribavirin for 12 weeks. The 12-week sofosbuvir/peginterferon/ribavirin regimen achieved SVR rates of 100% in genotype 2 patients and 91% in genotype 3 patients, an interesting finding. The 24-week regimen of sofosbuvir plus ribavirin achieved SVR rates of 50% in genotype 2 patients and 63% in genotype 3 patients.

For the first time, data were presented for HCV patients with decompensated liver disease with a sofosbuvir-based regimen. In a study by Afdhal and colleagues, sofosbuvir and ribavirin were administered for up to 48 weeks in both decompensated and compensated patients.²¹ Interim data on 25 patients showed that this regimen was efficacious in the decompensated population; all patients achieved a sustained response. The regimen was well tolerated. There also were improvements in the Model for End-Stage Liver Disease score, albumin level, and platelet counts. This study was the first to show that treatment in decompensated patients with HCV improved clinical status. The results are very exciting and should lead to further trials.

Kwo and associates presented data on post-liver transplant patients.²² HCV patients with genotype 1 received a regimen of the direct-acting antiviral agents ABT-450, ABT-267, and ABT-333 plus ribavirin. The regimen showed excellent

tolerability and high sustained response rates in this population. Among 26 patients in a preliminary analysis, the SVR12 rate was 96%.

Another important study was presented by Osinusi and colleagues on patients with HCV and HIV.²³ An interim report of a regimen of sofosbuvir and ledipasvir showed high efficacy. The SVR4 rate was 100%.

Conclusion

These important abstracts have provided insight into the best use of novel regimens that are currently available or that will likely be approved in the near future. Subsequent studies will provide data on how to optimize these regimens in special populations, such as patients with genotype 4, those who have failed previous therapy, those who have undergone liver transplant, and those with HIV.

Acknowledgment

Dr Flamm has performed research for AbbVie, Gilead, Vertex, BI, BMS, and Janssen. He is a consultant for AbbVie, Gilead, BMS, Janssen, and Merck.

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