Morgan Stanley does and seeks to do business with companies covered in Morgan Stanley Research. As a result, investors should be aware that the firm may have a conflict of interest that could affect the objectivity of Morgan Stanley Research. Investors should consider Morgan Stanley Research as only a single factor in making their investment decision.

For analyst certification and other important disclosures, refer to the Disclosure Section, located at the end of this report.
Company: Abbvie  
Drug: ABT-493 / ABT-530  
Abstract Number: THU-482

**Abstract Body**

**Background and Aims:** ABT-493 (protease inhibitor discovered by AbbVie and Enanta) and ABT-530 (NS5A inhibitor) are direct acting antivirals developed as a combination regimen for treatment of chronic hepatitis C virus genotype 1-6 infection. Pharmacokinetics of ABT-493 and/or ABT-530 were evaluated in subjects with normal hepatic function or hepatic impairment.

**Methods:** Classification of hepatic impairment was determined by Child-Pugh (CP) score (A, B, or C). Subjects with normal hepatic function or CP-A, CP-B, or CP-C (N = 6 per group) received single dose of ABT-530 120 mg alone, or with ABT-493 200 mg, or with ABT-493 300 mg in each period separated by ≥14-day washout; ABT-493 200 mg was not administered to CP-C subjects. Intensive pharmacokinetic sampling was performed following each dose. Log-transformed Cmax and AUC were analyzed under an ANCOVA analysis framework with hepatic function group as the primary factor of interest. Body weight, sex, and age were considered as possible covariates. For each dose level, ratios for model-estimated Cmax and AUC for each impairment group relative to the normal group were generated with corresponding 90% confidence intervals. Safety was evaluated through assessment of adverse events, vital signs, ECGs and clinical laboratory tests. Results: For ABT-493 300 mg + ABT-530 120 mg, central value ratios of AUC relative to normal subjects for ABT-493 were 1.33 (CP-A), 2.00 (CP-B), and 11.1 (CP-C) and for ABT-530 were 0.80 (CP-A), 1.26 (CP-B), and 2.11 (CP-C). For ABT-493 200 mg + ABT-530 120 mg, central value ratios of AUC for ABT-493 were 1.79 (CP-A) and 2.80 (CP-B) and for ABT-530 were 0.88 (CP-A) and 1.09 (CP-B). For ABT-530 120 mg, central value ratios of ABT-530 AUC were 1.51 (CP-A), 1.31 (CP-B), and 5.15 (CP-C). Cmax ratios were generally less than or similar to AUC. Adverse events (AEs) were mostly mild (Grade 1) and assessed as not related to study drugs. There were no severe or serious AEs, and no clinically significant changes from baseline in ECG measurements or hepatic laboratory measurements. Conclusions: Ongoing studies will evaluate the safety and efficacy of ABT-493 300 mg + ABT-530 120 mg in HCV-infected subjects with normal hepatic function or compensated cirrhosis (CP-A). Similar or lower doses may be evaluated in HCV-infected CP-B subjects. Future studies of ABT-493 and ABT-530 are not planned in HCV-infected CPC subjects.

**ENDURANCE-3: A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY TO COMPARE EFFICACY AND SAFETY OF ABT-493/ABT-530 TO SOFOSBUVIR CO-ADMINISTERED WITH DACLATASVIR IN ADULTS WITH HCV GENOTYPE 3 INFECTION**
**ENDURANCE-3: A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY TO COMPARE EFFICACY AND SAFETY OF ABT-493/ABT-530 TO SOFOSBUVIR COADMINISTERED WITH DACLATASVIR IN ADULTS WITH HCV GENOTYPE 3 INFECTION**

<table>
<thead>
<tr>
<th>Company</th>
<th>Abbvie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>ABT-493 / ABT-530</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>THU-482</td>
</tr>
</tbody>
</table>

**Abstract Body**  
Background and Aims: ABT-493 (protease inhibitor discovered by AbbVie and Enanta) and ABT-530 (NS5A inhibitor) are direct acting antivirals developed as a combination regimen for treatment of chronic hepatitis C virus genotype 1-6 infection. Pharmacokinetics of ABT-493 and/or ABT-530 were evaluated in subjects with normal hepatic function or hepatic impairment.

Methods: Classification of hepatic impairment was determined by Child-Pugh (CP) score (A, B, or C). Subjects with normal hepatic function, or CP-A, CP-B, or CP-C (N = 6 per group) received single dose of ABT-530 120 mg alone, or with ABT-493 200 mg, or with ABT-493 300 mg in each period separated by ≥14-day washout; ABT-493 200 mg was not administered to CP-C subjects. Intensive pharmacokinetic sampling was performed following each dose. Log-transformed Cmax and AUC were analyzed under an ANCOVA analysis framework with hepatic function group as the primary factor of interest. Body weight, sex, and age were considered as possible covariates. For each dose level, ratios for model-estimated Cmax and AUC for each impairment group relative to the normal group were generated with corresponding 90% confidence intervals. Safety was evaluated through assessment of adverse events, vital signs, ECGs and clinical laboratory tests. Results: For ABT-493 300 mg + ABT-530 120 mg, central value ratios of AUC relative to normal subjects for ABT-493 were 1.33 (CP-A), 2.00 (CP-B), and 11.1 (CP-C) and for ABT-530 were 0.80 (CP-A), 1.26 (CP-B), and 2.11 (CP-C). For ABT-493 200 mg + ABT-530 120 mg, central value ratios of AUC for ABT-493 were 1.79 (CP-A) and 2.80 (CP-B) and for ABT-530 were 0.88 (CP-A) and 1.09 (CP-B). For ABT-530 120 mg, central value ratios of ABT-530 AUC were 1.51 (CP-A), 1.31 (CP-B), and 5.15 (CP-C). Cmax ratios were generally less than or similar to AUC. Adverse events (AEs) were mostly mild (Grade 1) and assessed as not related to study drugs. There were no severe or serious AEs, and no clinically significant changes from baseline in ECG measurements or hepatic laboratory measurements. Conclusions: Ongoing studies will evaluate the safety and efficacy of ABT-493 300 mg + ABT-530 120 mg in HCV-infected subjects with normal hepatic function or compensated cirrhosis (CP-A). Similar or lower doses may be evaluated in HCV-infected CP-B subjects. Future studies of ABT-493 and ABT-530 are not planned in HCV-infected CPC subjects.
# HIGH EFFICACY OF ABT-493 AND ABT-530 IN HCV GENOTYPE 1 INFECTED PATIENTS WHO HAVE FAILED DIRECT-ACTING ANTIVIRAL-CONTAINING REGIMENS: THE MAGELLAN-I STUDY

<table>
<thead>
<tr>
<th>Company</th>
<th>Abbvie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>ABT-493 / ABT-530</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>GS11</td>
</tr>
</tbody>
</table>

**Abstract Body**

**Introduction:** There are limited HCV treatment options for patients with prior DAA treatment failure. We evaluated the efficacy and safety of the combination regimen of the NS3/4A protease inhibitor ABT-493 plus the NS5A inhibitor ABT-530 with or without ribavirin (RBV) in HCV genotype 1 (GT1)-infected patients without cirrhosis who have failed DAA-containing regimens that included a protease inhibitor and/or NS5A inhibitor, with or without an NS5B polymerase inhibitor.

**Material and Methods:** MAGELLAN-I is an ongoing phase 2, randomised, open-label study. Patients were randomized to receive once-daily ABT-493 (identified by AbbVie and Enanta) and ABT-530 at doses of 200 + 80 mg (Arm A), 300 + 120 mg + 800 mg RBV (Arm B), or 300 + 120 mg (Arm C), respectively, for 12 weeks. Patients who failed previous treatment for reasons other than breakthrough or relapse were excluded.

Efficacy was assessed by sustained virologic response (HCV RNA < 15 IU/mL) at post-treatment week 12 (SVR12). Deep sequencing (Illumina MiSeq) was performed on HCV NS3 and NS5A genes from samples collected from all patients at baseline, and at the time of virologic failure.

**Results:** Fifty patients were randomised, of whom 42 (84%) had GT1a infection and 33 (66%) had treatment experience with regimens that contained 2 or 3 DAAs. Deep sequencing revealed baseline resistance-associated variants (RAVs) in 41 (82%) patients, 15 in NS3, 10 in NS5A, and 16 with RAVs in both targets (Table). Arm A enrolment was stopped early to investigate higher doses of study drugs in other arms. Among patients with SVR12 data, SVR12 was achieved in 6/6 (100%) Arm A patients, 20/21 (95%) Arm B patients, and 19/20 (95%) Arm C patients. Two virologic failures were observed; 1 relapse in an Arm B patient with baseline NS5A RAVs, and 1 breakthrough at treatment week 8 in Arm C in a patient with Crohn’s disease on immune suppressant therapy, and with baseline NS3 and NS5A RAVs. The most common adverse events (AEs) were headache (28%), fatigue (26%), and nausea (20%). Two patients experienced serious AEs assessed as unrelated to study drug or RBV (breast cancer and femoral fracture). There were no grade 3 laboratory abnormalities or treatment discontinuations due to AE.
<table>
<thead>
<tr>
<th>Company</th>
<th>Abbvie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>ABT-493 / ABT-530</td>
</tr>
</tbody>
</table>

### Abstract Body

**100% SVR4 WITH ABT-493 AND ABT-530 WITH OR WITHOUT RIBAVIRIN IN TREATMENT-NAÏVE HCV GENOTYPE 3-INFECTED PATIENTS WITH CIRRHOSIS**
TARGETING MITOCHONDRIAL FUNCTION WITH THE BCL-2 INHIBITOR ABT-263 INCREASES THERAPY EFFICACY AND EVADES SORAFENIB RESISTANCE

Company: Abbvie  
Drug: ABT-263  
Abstract Number: FRI-035

Background and Aims: Multikinase inhibitor sorafenib has limited efficacy in the treatment of advanced hepatocellular carcinoma (HCC). The lack of positive results from other drugs, underscore the importance of identifying weaknesses in HCC biology that current approaches have not recognized. While mitochondrial damage caused by sorafenib has been previously reported, mitochondrial participation in sorafenib toxicity and HCC therapy has drawn little attention. Novel therapies are demanded to increase drug efficacy in HCC treatment. Methods: Hepatoma cell lines sensitive and with sorafenib resistance (HepG2 S/R and Hep3B S/R) were treated with sorafenib and Bcl2- inhibitors, and transfected with Bcl-2, Bcl-xL and Mcl-1 siRNAs. Western blots in total, cytosolic and mitochondrial extracts and qPCRs were performed. Mitochondrial functionality, caspase activation and apoptosis induction were analyzed in sorafenib-treated hepatoma cells. Tumor growth was determined in mice xenografts after subcutaneous injection of HepG2 S/R cells. Results: Sorafenib induction of mitochondrial dysfunction is mediated by blocking respiratory complex I activity and membrane potential that is followed by Mcl-1 depletion. Co-treatment of sorafenib-exposed hepatoma cells with ABT-263, (Navitoclax) a potent inhibitor of Bcl-xL and Bcl-2 in clinical trials for leukemia and solid tumors, strongly increased sorafenib-induced cell death. In a similar extent, Mcl-1 silencing sensitized hepatoma cells to ABT-263 supporting an important role for Mcl-1 in sorafenib efficacy. Moreover, ABT-263 potentiated sorafenib-mediated cell death via an apoptotic mechanism inducing cytochrome c release, PARP-1 cleavage and nuclear condensation. In addition, ABT-263 was equally effective to sensitize hepatoma resistant cell lines (Hep3B R and HepG2 R) to sorafenib exposure. Finally, in vivo administration of ABT-263 combined with sorafenib greatly potentiated sorafenib effects, decreasing subcutaneous tumor growth of HepG2 sensitive and resistant cells in nude mice. Conclusions: ABT-263, via inhibition of Bcl-2 and Bcl-xL, combined with sorafenib-induced reduction of Mcl-1 in hepatoma cells potentiates the mitochondrial vulnerability induced by sorafenib leading to apoptotic death, even in sorafenib-resistant cells. ABT-263 (Navitoclax), in combination with sorafenib administration is a therapeutic strategy to take into account in HCC management.
## ABT-493 AND ABT-530 COMBINATION DEMONSTRATED MINIMAL POTENTIAL FOR CYP-MEDIATED DRUG-DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Company</th>
<th>Abbvie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>ABT-493 / ABT-530</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>THU-229</td>
</tr>
</tbody>
</table>

### Abstract Body

**Background and Aims:** ABT-493 (protease inhibitor discovered by AbbVie and Enanta) and ABT-530 (NS5A inhibitor) are direct acting antivirals developed as a combination regimen for treatment of chronic hepatitis C virus genotype 1–6 infection. To evaluate the drug-drug interaction potential of ABT-493 and ABT-530 with drugs metabolized by cytochrome P450 (CYP) enzymes, pharmacokinetics of a cocktail of CYP probe substrates were evaluated when coadministered with ABT-493 + ABT-530. **Methods:** This was an open label study in 24 healthy adult subjects. Single oral doses of CYP probe substrates (CYP1A2: caffeine 100 mg; CYP2D6: dextromethorphan hydrobromide (HBr) 30 mg; CYP3A: midazolam 1 mg; CYP2C19: omeprazole 20 mg; and CYP2C9: tolbutamide 500 mg) were administered on Days 1 and 11. ABT-493 300 mg QD and ABT-530 120 mg QD were administered on Days 4 to 13. Intensive pharmacokinetic assessments were performed for CYP substrates and their relevant metabolites on Days 1 and 11 and for ABT-493 and ABT-530 on Day 10. The effects of ABT-493 + ABT-530 on CYP substrate pharmacokinetics were assessed by a repeated-measures analysis. Safety was evaluated through assessment of adverse events, vital signs, ECGs and clinical laboratory tests. **Results:** Compared to exposure of each substrate following administration of the cocktail alone, coadministration with multiple ABT-493 and ABT-530 doses slightly increased caffeine AUCinf by 35% and midazolam AUCinf by 27%, but did not affect Cmax for either substrate (≤11% difference); Cmax and AUCinf of omeprazole and tolbutamide were unaffected (≤20% difference); Cmax and AUCinf of dextromethorphan were 30% and 25% lower, respectively. Exposures of ABT-493 and ABT-530 when administered alone were similar to other studies in healthy subjects. All adverse events were Grade 1 (mild) in severity and most assessed as not related to any study drug. No clinically significant values of changes from baseline in ECG measurements or laboratory measurements were observed. **Conclusions:** ABT-493 and ABT-530 did not affect CYP2C9 or CYP2C19, did not inhibit CYP2D6, and weakly inhibited CYP1A2 and CYP3A. Significant drug-drug interactions are not expected with CYP1A2 or CYP3A substrates and therefore, no dose adjustment is needed for drugs metabolized by these 5 CYP enzymes when co-administered with ABT-493 and ABT-530.
PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF NEXT GENERATION DIRECT ACTING ANTIVIRALS ABT-493 AND ABT-530 IN SUBJECTS WITH RENAL IMPAIRMENT

Company: Abbvie
Drug: ABT-493 / ABT-530
Abstract Number: THU-230

Abstract Body: Background and Aims: ABT-493 (protease inhibitor discovered by AbbVie and Enanta) and ABT-530 (NS5A inhibitor) are once-daily next generation direct acting antivirals that have demonstrated high efficacy in combination against chronic hepatitis C virus genotype 1–6 infection. Both drugs lack significant renal clearance and may be candidates for treatment of HCV-infection in patients with severe- or end-stage renal disease (ESRD)—currently an unmet medical need. The objective of this Phase 1 study was to evaluate the pharmacokinetics of ABT-493 and ABT-530 in subjects with normal renal function or renal impairment.

Methods: Renal function was estimated as glomerular filtration rate (eGFR; MDRD equation) and groups of subjects were evaluated according to normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) mild (eGFR 60–89), moderate (eGFR 30–59), severe renal impairment (eGFR 15–29), or ESRD not yet on dialysis (eGFR < 15). Up to 8 subjects in each group received the single dose ABT-493 300 mg + ABT-530 120 mg combination and intense pharmacokinetic samples were collected up to 144 hours after dosing. For each analyte, regression analysis was performed on the logtransformed Cmax and AUC as a function of eGFR or creatinine clearance (CLcr) calculated via the Cockcroft-Gault equation. Body weight, sex, and age were considered as possible covariates. Ratios for model-estimated Cmax and AUC for each impairment group relative to the normal renal function group were generated with 90% confidence intervals. Safety was evaluated through assessment of adverse events, vital signs, ECGs and clinical laboratory tests. Results: Compared to subjects with normal renal function, ABT-493 and ABT-530 exposures in subjects with renal impairment were up to 10% (mild), 23% (moderate), 34% (severe) and 42% (ESRD) higher based on CLcr, and up to 15% (mild), 35% (moderate), 53% (severe), and 66% (ESRD) higher based on eGFR as markers of renal impairment. The t1/2 for ABT-493 and ABT-530 was unchanged and the percentage of ABT-493 or ABT-530 excreted in urine was very low (≤0.25%). Adverse events were mostly mild (Grade 1), no drugrelated severe or serious AEs were reported. There were no clinically significant ECG changes observed from baseline and the majority of changes in laboratory measurements were without clinical significance. Conclusions: No dose adjustment of ABT-493 and ABT-530 is needed in subjects with mild, moderate, severe or ESRD renal impairment not yet on dialysis.
PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF NEXT GENERATION DIRECT ACTING ANTIVIRALS ABT-493 AND ABT-530 IN SUBJECTS WITH HEPATIC IMPAIRMENT

Company: Abbvie
Drug: ABT-493 / ABT-530
Abstract Number: THU-231

Abstract Body: Background and Aims: ABT-493 (protease inhibitor discovered by AbbVie and Enanta) and ABT-530 (NS5A inhibitor) are direct acting antivirals developed as a combination regimen for treatment of chronic hepatitis C virus genotype 1-6 infection. Pharmacokinetics of ABT-493 and/or ABT-530 were evaluated in subjects with normal hepatic function or hepatic impairment.

Methods: Classification of hepatic impairment was determined by Child-Pugh (CP) score (A, B, or C). Subjects with normal hepatic function or CP-A, CP-B, or CP-C (N = 6 per group) received single dose of ABT-530 120 mg alone, or with ABT-493 200 mg, or with ABT-493 300 mg in each period separated by ≥14-day washout; ABT-493 200 mg was not administered to CP-C subjects. Intensive pharmacokinetic sampling was performed following each dose. Log-transformed Cmax and AUC were analyzed under an ANCOVA analysis framework with hepatic function group as the primary factor of interest. Body weight, sex, and age were considered as possible covariates. For each dose level, ratios for model-estimated Cmax and AUC for each impairment group relative to the normal group were generated with corresponding 90% confidence intervals. Safety was evaluated through assessment of adverse events, vital signs, ECGs and clinical laboratory tests. Results: For ABT-493 300 mg + ABT-530 120 mg, central value ratios of AUC relative to normal subjects for ABT-493 were 1.33 (CP-A), 2.00 (CP-B), and 11.1 (CP-C) and for ABT-530 were 0.80 (CP-A), 1.26 (CP-B), and 2.11 (CP-C). For ABT-493 200 mg + ABT-530 120 mg, central value ratios of AUC for ABT-493 were 1.79 (CP-A) and 2.80 (CP-B) and for ABT-530 were 0.88 (CP-A) and 1.09 (CP-B). For ABT-530 120 mg, central value ratios of ABT-530 AUC were 1.51 (CP-A), 1.31 (CP-B), and 5.15 (CP-C). Cmax ratios were generally less than or similar to AUC. Adverse events (AEs) were mostly mild (Grade 1) and assessed as not related to study drugs. There were no severe or serious AEs, and no clinically significant changes from baseline in ECG measurements or hepatic laboratory measurements.

Conclusions: Ongoing studies will evaluate the safety and efficacy of ABT-493 300 mg + ABT-530 120 mg in HCV-infected subjects with normal hepatic function or compensated cirrhosis (CP-A). Similar or lower doses may be evaluated in HCV-infected CP-B subjects. Future studies of ABT-493 and ABT-530 are not planned in HCV-infected CPC subjects.
ANALYSIS OF HCV GENOTYPE 2 AND 3 VARIANTS IN PATIENTS TREATED WITH COMBINATION THERAPY OF NEXT GENERATION HCV DIRECT-ACTING ANTIVIRAL AGENTS ABT-493 AND ABT-530

Company  Abbvie
Drug  ABT-493 / ABT-530
Abstract Number  THU-240
Abstract Body  Background and Aims: ABT-493 (NS3/4A protease inhibitor identified by AbbVie and Enanta) and ABT-530 (NS5A inhibitor) are next generation HCV direct-acting antiviral agents. Results from Part 1 of the SURVEYOR-I and -II dose-ranging studies demonstrated that co-administration of ABT-493 (200–300 mg) and ABT-530 (40–120 mg) ± ribavirin for 12 weeks achieved high sustained virologic response (SVR) in patients with HCV GT1, GT2, or GT3 infection. In this report we present the characterization of GT2 and GT3 variants detected in samples from Part 1 of the SURVEYOR-II study. Methods: Population sequencing was performed on the NS3 and NS5A genes from all baseline (BL) samples, and the first available sample after virologic failure (VF) with HCV RNA ≥1000 IU/mL. Sequences were examined for the presence of variants at positions where resistance to drugs in the protease or NS5A inhibitor class is known to occur: NS3 positions 56, 155, 156, 166 (GT3 only), and 168, and NS5A positions 24, 28, 29, 30, 31, 32, 58, 92, and 93. Results: For BL samples from GT2-infected patients (n = 74), 36 had M31 in NS5A, a common polymorphism that confers resistance to a number of NS5A inhibitors but not to ABT-530. In addition, 6 patients had other BL NS5A variants, by themselves or in combination with M31, and no patients had variants in both targets at BL. Irrespective of the presence of BL variants, all GT2-infected patients, except 1 lost to follow-up (LTFU), achieved SVR12. For GT3-infected patients (n = 121), 17 had NS3 variants, 18 had NS5A variants, and 5 had variants in both targets at BL. Seven GT3-infected patients experienced VF; only 1 of these VFs (a relapse) occurred in an IFN/RBV experienced patient receiving the 300 mg/120 mg ABT-493/ABT-530 combination. For this patient, no NS3 variants and 1 NS5A variant (A30K) were detected at BL; a double NS3 variant (Y56H + Q168R) and a double NS5A variant (A30K + Y93H) were detected at VF. The other 6 VF patients were treated with lower, suboptimal combination doses; variant analysis will be presented. Conclusions: All GT2-infected patients, except 1 LTFU, achieved SVR12 regardless of presence or absence of BL NS3 or NS5A variants. For GT3-infected patients, since VF occurred in only 1 patient receiving 300 mg/120 mg ABT-493/ABT-530, the dose chosen for further studies, evaluation of more GT3-infected patients receiving this dose will be needed in order to fully assess the impact of BL variants on treatment outcome.
HIGH EFFICACY AND FAVORABLE SAFETY OF ABT-493 AND ABT-530 CO-ADMINISTRATION FOR 12 WEEKS IN HCV GENOTYPE 1-INFECTED PATIENTS WITH CIRRHOSIS (SURVEYOR-I)

Company: Abbvie
Drug: ABT-493 / ABT-530
Abstract Number: SAT-135

Abstract Body: Background and Aims: Next generation direct-acting antivirals (DAAs), including ABT-493, an NS3/4A protease inhibitor (identified by AbbVie and Enanta) and ABT-530, an NS5A inhibitor, have demonstrated potent antiviral activity against all major HCV genotypes (GTs) in vitro, with little or no loss of potency against common resistance-associated variants. Furthermore, the ABT-493/ ABT-530 combination was well-tolerated and achieved high sustained virologic response (SVR) rates in patients with HCV GT1, GT2 and GT3 infection without cirrhosis (SURVEYOR-I/II, Part 1). Here we present data from Part 2 of the SURVEYOR-I study, evaluating the safety and efficacy of ABT-493 and ABT-530 administered for 12 weeks in HCV GT1-infected patients with compensated cirrhosis. Methods: Treatment-naïve or pegylated interferon/ribavirin treatment-experienced patients with cirrhosis received ABT-493 200 mg + ABT-530 120 mg once daily for 12 weeks. Cirrhosis was determined by either liver biopsy (Metavir F4), Fibroscan (liver stiffness >14.6 KPa) or serum markers (Fibrotest score ≥0.75 and an APRI > 2). SVR at post-treatment week 12 (SVR12; HCV RNA levels determined using Roche COBAS TaqMan® RT-PCR assay [lower limit of detection of 15 IU/mL and lower limit of quantification of 25 IU/ mL]) and safety are reported. Results: A total of 27 patients were enrolled and the population was 74% male, 89% white, 74% GT1a, 85% non-CC IL28B, 26% HCV treatment-experienced, and all reported baseline fibrosis scores of F4. The median (range) HCV RNA log10 IU/mL was 6.7 (5.6–7.3), and 93% had HCV RNA ≥6,000,000 IU/mL at baseline. SVR12 was achieved in 26 out of 27 (96%) patients, with one patient experiencing relapse at post-treatment week 4. All adverse events (AEs) were deemed mild or moderate in severity, with no patients reporting severe or serious AEs considered related to study drugs. No patients discontinued treatment prematurely due to AEs and the most frequent AEs reported in >10% of patients were fatigue (11%) and headache (11%). No clinically meaningful abnormal liver function or other laboratory results were observed. Conclusions: Treatment with the IFN- and ribavirin-free combination of next generation HCV DAAs, ABT-493 and ABT-530, was welltolerated and achieved high SVR12 rates of 96% following a 12-week treatment regimen in GT1-infected patients with compensated cirrhosis regardless of baseline viral load or prior treatment history.
100% SVR4 AND FAVORABLE SAFETY OF ABT-493 + ABT-530 ADMINISTERED FOR 12 WEEKS IN NON-CIRRHOTIC PATIENTS WITH GENOTYPES 4, 5, OR 6 INFECTION (SURVEYOR-I)

**Company**  
Abbvie

**Drug**  
ABT-493 / ABT-530

**Abstract Number**  
SAT-137

**Abstract Body**  
Background and Aims: Next-generation HCV direct-acting antivirals ABT-493, an NS3/4A protease inhibitor identified by AbbVie and Enanta, and ABT-530, an NS5A inhibitor, demonstrated potent pangenotypic in vitro antiviral activity, with a high barrier to resistance and maintenance of activity against common resistance-associated variants. Part 2 of the SURVEYOR-I study evaluates the efficacy and safety of ABT-493 and ABT-530 co-administered for 12 weeks in non-cirrhotic patients with HCV genotypes 4, 5, or 6 infection. Methods: Treatment-naïve or pegylated interferon/ribavirin treatment-experienced patients received once-daily ABT-493 300 mg + ABT-530 120 mg for 12 weeks. Sustained virologic response at post-treatment week 4 (SVR4; HCV RNA measured using COBAS TaqMan® RT-PCR [lower limit of detection of 15 IU/mL and lower limit of quantitation of 25 IU/mL]) and safety data are reported. Results: A total of 34 patients with genotype 4 (n = 22; 65%), 5 (n = 1; 3%), or 6 (n = 11; 32%) infection were enrolled: 53% male, 59% white, 62% had non-CC IL28B, and 15% were treatment-experienced. The median (range) HCV RNA log10 IU/mL was 6.4 (4.6–7.4) at baseline, and 35% of patients had HCV RNA ≥6,000,000 IU/mL. SVR4 was achieved by all 34 (100%) patients; SVR at post-treatment week 12 (SVR12) and baseline resistance data will be available for presentation. Adverse events (AEs) reported were deemed mostly Grade 1 (mild) in severity, with most common AEs being headache, diarrhea, and fatigue. No Grade 3 (severe) or higher AEs, serious AEs, premature discontinuations due to AEs were reported. While receiving therapy, no liver function or other laboratory abnormalities were observed. Conclusions: The combination of highly potent next generation direct-acting antivirals ABT-493 and ABT-530 was well tolerated and demonstrated 100% SVR4 in non-cirrhotic patients with genotype 4, 5, or 6 infection. These results along with previously reported promising efficacy in GT1, 2, and 3 infection establish potent clinical pangenotypic activity of this RBV-free once daily ABT-493 + ABT-530 regimen.
HIGH SVR RATES WITH THE COMBINATION OF ABT-493 + ABT-530 FOR 8 WEEKS IN NON-CIRRHOTIC PATIENTS WITH HCV GENOTYPE 1 OR 2 INFECTION

Company: Abbvie  
Drug: ABT-493 / ABT-530  
Abstract Number: SAT-157

Abstract Body: Background and Aims: Hepatitis C virus (HCV) direct-acting antivirals (DAAs), ABT-493 (NS3/4A protease inhibitor identified by AbbVie and Enanta) and ABT-530 (NS5A inhibitor), demonstrated potent pangenotypic antiviral activity in vitro, with a high barrier to resistance and maintenance of activity against common variants. In Part 1 of the SURVEYOR-I and SURVEYOR-II studies, ABT-493 + ABT-530 for 12 weeks was well tolerated and achieved sustained virologic response (SVR) rates between 97–100% in non-cirrhotic patients with HCV genotype (GT) 1 or 2 infection. In Part 2 of these studies, ABT-493 + ABT-530 was co-administered for a shorter duration of 8 weeks. Methods: Non-cirrhotic treatment-naïve patients or pegylated interferon/ribavirin treatment-experienced non-responders received once-daily ABT-493 300 mg + ABT-530 120 mg for 8 weeks. HCV RNA <25 IU/mL at post-treatment weeks 4 (SVR4) and 12 (SVR12) and safety are reported. Results: In Part 2 of SURVEYOR-I and -II, 34 patients with GT1 infection (71% GT1a; 68% non-CC IL28B genotype; 15% treatment-experienced) and 54 patients with GT2 infection (70% GT2b; 59% non-CC IL28B genotype; 13% treatment-experienced) were enrolled, respectively. Mean baseline HCV RNA log10 IU/mL ± standard deviation was 6.3 ± 1.1 for GT1-infected patients and 6.6 ± 0.8 for GT2-infected patients, with 38% and 57% of patients who had baseline levels ≥6 M IU/mL, respectively. SVR12 was achieved by 97% (33/34) of GT1-infected patients. SVR4 was achieved by 98% (53/54) of GT2-infected patients (SVR12 data will be available for presentation). There have been no virologic failures to date. One GT1-infected patient discontinued study prematurely at week 4 (with undetectable HCV RNA) due to a non-DAA related serious adverse event (AE) of abdominal cancer of unknown origin and subsequently died prior to reaching the SVR12 time point. The GT2-infected patient without SVR4 was lost to follow up after week 6, when HCV RNA was not detected. There were no other discontinuations due to AEs. Across both studies, AEs were mostly mild (Grade 1), with the most common AEs being fatigue and headache. Conclusions: The combination of ABT-493 and ABT-530 administered for 8 weeks in non-cirrhotic patients with HCV GT1 or GT2 infection was well tolerated and achieved SVR rates of 97–98%, with no virologic failures to date, regardless of baseline viral load or prior treatment history.
SAFETY OF ABT-493 AND ABT-530 CO-ADMINISTERED IN PATIENTS WITH HCV GENOTYPE 1 – 6 INFECTION: RESULTS FROM THE SURVEYOR-I AND SURVEYOR-II STUDIES

Company: Abbvie

Drug: ABT-493 / ABT-530

Abstract Number: SAT-239

Abstract Body: Background and Aims: The combination of next-generation HCV direct-acting antivirals, ABT-493 (NS3/4A protease inhibitor identified by AbbVie and Enanta) and ABT-530 (NS5A inhibitor), demonstrated high efficacy across the 6 major HCV genotypes (GTs) in the ongoing phase 2 SURVEYOR-I and -II studies. The safety profile in all patients who have evaluations at 4 weeks after 8 or 12 weeks of treatment are reported. Methods: Non-cirrhotic or cirrhotic patients, who were either treatment-naïve or pegylated interferon/RBV treatment-experienced, received once-daily ABT-493 + ABT-530 at respective doses of 300/120, 200/120, 200/40, ±RBV for 8 or 12 weeks. Adverse event (AE) monitoring and clinical laboratory testing occurred throughout the treatment and post-treatment periods. Safety analyses included all patients who received at least one dose of study drugs. Results: In SURVEYOR-I and SURVEYOR-II, 369 patients were included in this safety analysis: 38% GT1 (including 27 patients with compensated cirrhosis), 20% GT2, 33% GT3, and 9% with GT4, 5, or 6 infection. Across GTs, doses received for ABT-493/ABT-530 were 300/120 mg (n = 123), 200/120 mg (n = 121), 200/120 mg + RBV (n = 56), and 200/40 mg (n = 69). Across the studies, 253 (69%) of all patients experienced AEs, with the majority being mild (Grade 1) in severity. AEs occurred at a similar frequency across RBV-sparing dose combinations. Overall, 6 (2%) patients had serious AEs (none were considered related to study drugs), 3 (1%) patients, including 2 who received RBV, discontinued study drugs early due to AEs, and one death was reported during the study (not related to treatment). The most common AEs reported in all patients were fatigue (18%), headache (14%), and nausea (14%). Five patients developed Grade 2 anemia, four of whom received RBV. No patients experienced treatment-emergent ALT elevations ≥2 × ULN after reaching the ALT nadir. One GT3-infected patient had a severe (Grade 3) increase in CPK and AST after intense physical activity, which was resolved during treatment and considered not related to study drugs. Conclusions: In the SURVEYOR-I and SURVEYOR-II studies, ABT-493 + ABT-530 ± RBV was safe and well tolerated by treatment-naïve or -experienced patients across the 6 major HCV GTs. The frequency of AEs, which were mostly mild and tolerated, was comparable across dose combinations.

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>ABT-493 300 mg + ABT-530 120 mg</th>
<th>ABT-493 200 mg + ABT-530 120 mg</th>
<th>ABT-493 200 mg + ABT-530 120 mg + RBV (n=56)</th>
<th>ABT-493 200 mg + ABT-530 40 mg (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>79 (64)</td>
<td>77 (64)</td>
<td>48 (85)</td>
<td>49 (71)</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 (severe) AEs</td>
<td>3 (2)</td>
<td>6 (5)</td>
<td>5 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Study drug-related Grade 3 (severe) AEs</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Study drug-related serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs m &gt;10% of patients</td>
<td>Fatigue</td>
<td>18 (15)</td>
<td>20 (17)</td>
<td>22 (39)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>14 (11)</td>
<td>14 (12)</td>
<td>12 (21)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>11 (9)</td>
<td>12 (10)</td>
<td>19 (34)</td>
</tr>
</tbody>
</table>
OMBITASVIR (ABT 267), RITANAVIR BOOST WITH DASTASBUVIR (ABT 333) AND PRATASPRAVIR (ABT 450) WITH OR WITHOUT RIBAVIRIN (RBV) IN G1 SPECIAL POPULATION IN HEMODIALYSIS (HD) IN CHRONIC HEPATITIS C (HCV) PATIENTS. DROP C TRIAL

Company: Abbvie
Drug: Ombitasvir / Ritanavir / Prataspravir
Abstract Number: SAT-237

Abstract Body:

Background and Aims: Chronic Hepatitis C (CHC) is a global epidemic in the USA with a prevalence of 2.8% and an incidence of 3.3% in end-stage renal disease (ESRD) in hemodialysis (HD) population. CHC in ESRD with HD has a significant higher fibrotic state and accelerated cirrhosis with decompensation and higher rate of hepatocellular carcinoma (HCC). The mortality and hazard ratio of chronic hepatitis C in ESRD on HD relative to death risk is 1.79% and post renal transplant graft failure is 1.56%. Prior DAA’s with Interferon and Ribavirin achieved 63% SVR in 48 weeks. Primary Objective: To show the efficacy of the triple regimen (Paritaprevir, Ritonavir and Ombitasvir) by obtaining SVR12. Secondary Objectives: Safety, tolerability. Methods: Thirty Six (36) patients (18 cirrhots and 18 noncirrhots) were recruited from 4 dialysis centers across Brooklyn; in patients undergoing hemodialysis with chronic hepatitis C; genotype 1. The patients were divided into two groups: group A (n = 18) with cirrhosis and group B (n = 18) with no cirrhosis. Group A: Ombitasvir (Abt 267) + Ritanavir + Dastasbuvir (Abt 333) + Prataspravir (Abt 450); with 200 mg daily of RBV. Group B: Ombitasvir (Abt 267) + Ritanavir + Dastasbuvir (Abt 333) + Prataspravir (Abt 450); without RBV. Patient characteristics:

Conclusions: This study demonstrates a high SVR with a very short course DAA’s in HCV in patients on HD. Role of DAA’s in ESRD patients on HD in CHILD A cirrhots have encouraging SVR rates; though carries a risk of higher relapse rate despite daily modified doses of RBV. Overall, the drugs were well tolerated with minimal side events and without treatment failure.
HIGH SVR RATES WITH ABT-493 + ABT-530 CO-ADMINISTERED FOR 8 WEEKS IN NON-CIRRHOTIC PATIENTS WITH HCV GENOTYPE 3 INFECTION

<table>
<thead>
<tr>
<th>Company</th>
<th>Abbvie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>ABT-493 / ABT-530</td>
</tr>
</tbody>
</table>

**Abstract Number**

**Abstract Body**
### PAN-GENOTYPIC EVALUATION OF AL-335, A CLINICAL STAGE URIDINE ANALOGUE INHIBITOR OF HEPATITIS C VIRUS POLYMERASE

<table>
<thead>
<tr>
<th>Company</th>
<th>Alios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>AL-335</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>THU-226</td>
</tr>
</tbody>
</table>

**Abstract Body**

Background and Aims: AL-335 is a novel uridine based nucleotide analogue that is currently being evaluated for the treatment of chronic hepatitis C in Phase 2 clinical trials. The nucleoside triphosphate of AL-335 is a potent inhibitor of the hepatitis C virus genotype-1b NS5B polymerase. In this study, we compared the inhibition potencies of the nucleoside triphosphates of AL-335 and sofosbuvir against the RNA polymerase of other hepatitis C virus genotypes. Methods: The nucleoside triphosphates of AL-335 and sofosbuvir were tested for inhibition potency against recombinant NS5B from all six hepatitis C virus genotypes. Single nucleotide incorporation assays were conducted under pre-steady state kinetics to measure the efficiency of incorporation of AL-335 and sofosbuvir nucleoside triphosphates by NS5B. Molecular modelling was conducted to understand differences in NS5B active site binding interactions between AL-335 and sofosbuvir nucleoside triphosphates. Results: In biochemical assays, AL-335 nucleoside triphosphate was a potent pan-genotypic inhibitor of the NS5B polymerase with halfmaximal inhibitory concentration values ranging from 90 to 180 nM, genotype-3 being the most sensitive (half-maximal inhibitory concentration = 90 nM, inhibitory constant = 35 nM). In comparison, sofosbuvir nucleoside triphosphate was significantly less potent against the genotype-3 enzyme, with an inhibitory constant of 160-175 nM depending on the genotype-3 virus strain. The improved inhibition potency of AL-335 nucleoside triphosphate compared to sofosbuvir nucleoside triphosphate could be explained using pre-steady state kinetics of single nucleotide incorporation. In this assay, the level of enzyme discrimination compared to natural uridine-5’-triphosphate was 14-fold for AL-335 nucleoside triphosphate, versus 136-fold for sofosbuvir nucleoside triphosphate. This indicates that AL-335 nucleoside triphosphate is a 10-fold better substrate for genotype-3 NS5B than sofosbuvir nucleoside triphosphate. The interaction between AL-335 nucleoside triphosphate and the polymerase of genotype-4 to −6 will be presented at the meeting. Conclusions: AL-335 is a next-generation uridine based nucleotide analogue whose triphosphate is up to 10-fold more potent than sofosbuvir nucleoside triphosphate against the polymerase of hard-to-treat HCV genotype-3. AL-335 is advancing in Phase 2 studies as part of a combination therapy for the treatment of chronic hepatitis C.
A ONCE-DAILY PANGENOTYPIC NUCLEOTIDE HCV POLYMERASE INHIBITOR, DEMONSTRATES POTENT ANTIVIRAL ACTIVITY OVER 7 DAYS IN TREATMENT-NAÏVE GENOTYPE 1-4 PATIENTS

Company            Alios
Drug                AL-335
Abstract Number     THU-228

Abstract Body
Background and Aims: AL-335, a uridine nucleotide analog, is being developed as an oral anti-HCV therapy. An ongoing randomized, double-blind, placebo-controlled study is being conducted to assess the safety, and antiviral activity of AL-335 in treatment-naïve subjects with GT1-6 chronic hepatitis C (CHC). Methods: 6-8 cohorts of 10 subjects with GT1-6 CHC will be randomized to receive AL-335 (400 mg or 800 mg) or placebo in a 4:1 ratio for 7 days. Subjects were followed for an additional 14 days after completion of dosing. HCV RNA samples were obtained at baseline and at multiple time points during treatment and analyzed using COBAS® TaqMan® HCV Test (Version 2.0, Roche). Plasma for resistance monitoring was also obtained. Plasma samples were analyzed by a LC/MS/MS method for pharmacokinetics of AL-335 and metabolites. Results: To date, 52 subjects with GT1-4 CHC have been enrolled so far including 43 males and 9 females; 30 were GT1b (including 10 subjects with compensated cirrhosis), 10 were GT2, 10 were GT3, and 2 were GT4; 20/52 had IL28B CC genotypes. Mean baseline HCV RNA concentrations ranged from 5.90 to 6.53 log10 IU/mL. There was a rapid reduction in HCV RNA concentrations in all of the treatment groups. The maximal mean reduction after 7 days of dosing for the AL335 400 mg group was −2.76 log10 IU/mL. The maximal mean reduction after 7 days of dosing for the GT1, 2 and 3 groups receiving AL-335 800 mg was −4.00, −4.46 and −4.72 log10 IU/mL (Figure 1). No on treatment breakthroughs were observed. Reductions in ALT concentrations were also seen in subjects with elevated ALT concentrations at baseline. Additional data from 2 ongoing cohorts of subjects with compensated cirrhosis and GT4 infection will be presented. The plasma PK of AL-335 and its metabolites confirmed rapid uptake into the liver. Plasma concentrations of AL-335, the prodrug, were generally low with the parent nucleoside observed as the major circulating metabolite. Initial safety data indicates that both doses of AL-335 were well tolerated. Mild to moderate headache was the most frequently observed adverse event on treatment. No SAEs were reported and no subjects prematurely discontinued treatment. No clinically significant changes in vital signs, ECG readings or laboratory abnormalities were observed. Conclusions: Preliminary data demonstrate that treatment with AL-335 resulted in a rapid reduction of viral load over a seven day period. AL-335 was well tolerated with no SAEs or dose-limiting AEs reported.
HEPATITIS DELTA VIRUS KINETICS UNDER THE PRENYLATION INHIBITOR LONAFARNIB SUGGEST HDV-MEDIATED SUPPRESSION OF HBV REPLICATION

<table>
<thead>
<tr>
<th>Company</th>
<th>Eiger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Lonafarnib</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>FRI-111</td>
</tr>
</tbody>
</table>

Abstract Body

Background and Aims: The prenylation inhibitor lonafarnib (LNF) is the first antiviral treatment against hepatitis D virus (HDV). HDV-directed antiviral treatment may provide novel information about HDV kinetics and the interplay between HDV and hepatitis B virus (HBV). Methods: HDV RNA, HBV DNA, HBsAg and ALT kinetics data were obtained from a phase 2 study of 5 LNF-based treatments (n = 3 per group): LNF 200 mg bid [12 wks], 300 mg bid [12 wks], LNF 100 mg tid [5 wks], LNF 100 mg bid in combination with 100 mg ritonavir qd [8 wks] or pegylated interferon (pegIFN) 180 μg qw [8 wks]. None of the patients received anti-HBV treatment with nucleos(t)ide analogues. Serum samples for kinetics analysis were obtained before treatment and on days 1, 2, 3, 7, 14 and then every 2 weeks until end of treatment (EOT). Results: The kinetics pattern of HDV RNA consisted of two phases: a 1st rapid decline with median slope of 0.91 log/wk/mL [interquartile range (IQR):0.43], that lasted 1.5 wks [IQR:1.4], followed by undetectable [n = 1] or slower 2nd decline phase [n = 3], plateau [n = 6] or rebound [n = 5]. Patients who were treated with LNF 300 mg bid or LNF 100 mg bid + ritonavir had either 2nd phase decline or plateau. While in 7 patients (including all subjects treated with pegIFN) HBV remained at pre-treatment levels, in 8 patients an increase in HBV was evident with a median increasing slope of 0.32 log/wk/mL [IQR:0.15]. The median ALT level at EOT, 43 U/L [IQR:36] was significantly reduced from a median pretreatment level of 82 U/L [IQR:118] (p = 0.03). The rise in HBV DNA of up to 5 log10 IU/mL from pre-treatment level was not associated with a concomitant rise in ALT levels (p = 0.8). There was significant positive correlation between the reduction in HDV and ALT from baseline to EOT (r = 0.55, p = 0.03). HBsAg levels did not change during treatment. Conclusions: Treatment with LNF provides a novel window into the dynamics between HDV and HBV replication. The inverse relationship between HDV and HBV observed in about 50% of patients is consistent with viral interference in which HDV suppresses HBV in co-infected patients. The decline in ALT levels in all but two patients combined with the re-emergence of HBV is consistent with LNF exerting a direct effect on blocking HDV replication/assembly rather than promoting the death of productively infected cells.
# PHARMACOKINETICS AND PHARMACODYNAMICS MODELING OF LONAFARNIB IN PATIENTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION

<table>
<thead>
<tr>
<th>Company</th>
<th>Eiger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Lonafarnib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abstract Number</th>
<th>FRI-115</th>
</tr>
</thead>
</table>

**Abstract Body**

Background and Aims: The prenylation inhibitor lonafarnib (LNF) is a potent antiviral agent providing a breakthrough for the treatment of hepatitis delta virus (HDV) and an opportunity to further characterize HDV dynamics during treatment (Phase 2a double-blinded randomized placebo-control study: Lancet Infect Dis 2015;15:1167–1174). Here, we used modeling to estimate the pharmacokinetic (PK), pharmacodynamics (PD) and viral kinetic (VK) parameters to further describe the interaction between the drug, host, and virus. Methods: Patients were treated with LNF 100 mg twice daily (bid) (Group 1) or 200 mg twice daily (bid) (Group 2) for 28 days. PK samples were collected at 0, 6, 12, 18, 24, 36, 48, 60, 72 h relative to the first dose; at 0, 0.25, 0.5, 1, 2, 4, 6, 12 h on day 14 (steady-state); and on days 21 and 28 (pre-dose). VK samples were collected at 0, 6, 12, 18 h relative to the first dose and on days 1, 1.5, 2, 3, 7, 14, 21, 28 (pre-dose). We simultaneously estimated the parameters of the PK, PD and VK model, using the stochastic approximation of the expectation-maximization algorithm implemented in MONOLIX 4.3.2. Results: The LNF PK was described by a 1-compartment model with lag-time, 1st order absorption (ka) and 1st order elimination (k). After a delay of 0.56 h (Relative Standard Error, RSE = 16%), ka was estimated as 0.43 h⁻¹ (RSE = 28%), k as 0.045 h⁻¹ (RSE = 12%) and the volume of distribution as 212 L (RSE = 14%). All PK parameters exhibited inter-individual variability (IIV), ranging from 35% (RSE = 25%) for the elimination rate to 85% (RSE = 26%) for the absorption rate. This led to an average steady-state LNF concentration of 860 ng/mL and 1734 ng/mL in Groups 1 and 2, respectively. The LNF concentration that decreased HDV production by 50% EC₅₀ was 227 ng/mL (RSE = 26%) with a Hill factor of 1.48 (RSE = 7%). We found that IIV for EC₅₀ was 62% (RSE = 23%), translating into a drug efficacy of 87.7% and 95.2% at steady-state for Groups 1 and 2, respectively. The serum virus clearance rate was 0.37 d⁻¹ (RSE = 10%) which corresponds to a virus half-life of 1.87 d. Conclusions: The current study provides the first insights into LNF PK and PD in chronically HDV-infected patients and suggests that steady-state LNF concentration above 1002 ng/mL could achieve 90% efficacy in blocking HDV production.
LIVER STIFFNESS MEASUREMENT BY TRANSIENT ELASTOGRAPHY FOR THE PREDICTION OF FIBROSIS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS IN A RANDOMIZED TRIAL OF SIMTUZUMAB

Background and Aims: Our objective was to assess the diagnostic performance of liver stiffness measurement (LSM) by transient elastography (TE) for the prediction of fibrosis in patients with primary sclerosing cholangitis (PSC). Methods: Liver stiffness was measured by TE (FibroScan, Echosens, Paris, France) in subjects with PSC enrolled in a sub-study of a phase 2b trial of simtuzumab, a monoclonal antibody directed against lysyl oxidase-like-2 (LOXL2). Liver fibrosis was staged according to the Ishak classification and hepatic collagen in sirius red-stained biopsies was quantified via computer-assisted morphometry. The correlations between liver stiffness and Ishak fibrosis stage, hepatic collagen, serum fibrosis markers (LOXL2, FibroTest, ELF), and Mayo Risk Score were determined. The diagnostic performance of TE for predicting bridging fibrosis (Ishak stages 3–6 vs. 0–2) and cirrhosis (stages 5–6 vs. 0–4) was determined using AUROCs and compared with serum fibrosis markers; sensitivity analyses were conducted according to biopsy length (≥ vs. < 0.001). For bridging fibrosis, the AUROC of TE was 0.79 (95% CI 0.67–0.91); at a cut-off of ≥9.6 kPa, TE was 67% sensitive, 72% specific, and had positive (PPV) and negative predictive values (NPV) of 69% and 70%, respectively. For cirrhosis, the AUROC of TE was 0.95 (95% CI 0.88–1.00); the sensitivity, specificity, PPV, and NPV of TE at a cut-off of ≥14.4 kPa were 100%, 82%, 40%, and 100%, respectively. The AUROCs for TE were similar to those of LOXL2, FibroTest, and ELF, and did not differ according to biopsy length (data not shown). Conclusions: Liver stiffness measurement by TE can effectively exclude PSC-related cirrhosis, but has sub-optimal accuracy for the prediction of bridging fibrosis.
EFFICACY AND SAFETY OF SIMEPREVIR PLUS SOFOSBUVIR PLUS RIBAVIRIN FLAT DOSE IN A POPULATION OF NAIVE AND EXPERIENCED HCV GENOTYPE 1 CIRRHOTIC ELDERLY PATIENTS: A REAL WORLD EXPERIENCE FROM CLEO GROUP

**Company**

Gilead

**Drug**

Sofosbuvir

**Abstract Number**

THU-002

**Abstract Body**

Methods: One hundred and seventy-five G1 naive or experienced HCV infected patients with Child Pugh A liver cirrhosis were treated with SOF plus SMV plus a flat dose of RBV. The patients were divided into 2 Group by age: Group I (65 years n = 79). Sustained virological response (SVR) was evaluated 4 (SVR4) and 12 weeks (wks) (SVR12) after end of therapy. Multiple comorbidities, adverse events (AE) and severe adverse events (SAE) were evaluated and compared between the two Groups of patients. Results: Seventy–nine patients were older that 65 years (yrs) (mean 72 ± 5 yrs) while 96 were younger (mean 56 ± 5 yrs). The patients were treated with an association of SOF 400 mg/day plus SMV 150 mg/day plus RBV flat dose (800 mg/day) for a duration of 12 wks. Most were male (52%), caucasian (100%) and treatment experienced (65%) patients. Diabetes was more frequent in Group II patients respect to group I (25.3% vs 13.5% p < 0.03), while systemic hypertension, hypercholesterolemia and cryoglobulinemia had a similar incidence in the two Groups of patients. Hepatocellular carcinoma was more frequent in Group II patients respect to Group I (12.7% vs 1.0% p < 0.002). SVR4 and SVR12 was achieved respectively in 167/175 and 150/158 of total patients. SVR12 was similar between the two Groups of patients (Group I 85/90 patients vs Group II 65/68 patients, p = 0.5). Adverse events (AEs) were similar in the two group of patients except for grade 2 anemia that was more frequent in patients of Group II respect to Group I (31% vs 18% p < 0.05). Grade 3 anemia was similar between the two Groups (Group I 3.1% vs Group II 4.05% p = 0.9). No difference between the two Groups was reported regarding SAE (1% vs 0% ns). Conclusions: SOF plus SMV plus a flat dose of RBV can be used safely in patients aged more than 65 years. Furthermore this regimen presents similar high efficacy in term of SVR12 in the two Groups of patients analyzed.
Background and Aims: The currently approved treatment for pts with GT-2 infection is the combination of SOF/RBV. In US, comparing real life to phase III studies, reduced SVR rates were shown. Moreover, although EASL guidelines advice, as maximum, a duration of 20 wks, it is debated whether treatment should be further extended to 24 wks, in order to prevent relapse. In a cohort of HCV GT-2 patients treated from January 2015, according to DAA approval in Italy, efficacy results of SOF/RBV were evaluated. Methods: 215 patients with GT-2 and Metavir F3/4 fibrosis stage were eligible to treatment; 20 RBV ineligible were excluded, all the others received SOF/RBV for 12 or 20 wks according to absence/presence of cirrhosis. Efficacy was evaluated based on HCV RNA at post-treatment wk 12 by ABBOTT HCVRNA, LLQ severe obesity were present in 51.4%. Pts were continued on PPI (n = 43), blood hypertension medications (n = 31), oral antidiabetics (n = 10) without DDI. On treatment, end of treatment (EOT) and SVR rates overall, and by cirrhosis are reported below. Conclusions: In Italy, high rates of SVR are observed in GT-2 patients with stage F3/F4, despite old age, co-morbidities and concomitant drug assumption, provided they were treated, based on absence/presence of cirrhosis, for 12 or 20 wks. No need for an extended duration of treatment can be supported by this study.

<table>
<thead>
<tr>
<th>No.</th>
<th>Wk 4</th>
<th>Wk 8</th>
<th>EOT</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3 (n = 71)</td>
<td>53 (75%)</td>
<td>55 (77%)</td>
<td>67* (94%)</td>
<td>70 (98%)</td>
</tr>
<tr>
<td>F4 (n = 69)</td>
<td>37 (54%)</td>
<td>41 (59%)</td>
<td>69* (100%)</td>
<td>68 (98%)</td>
</tr>
<tr>
<td>CPT A5 (n = 25)</td>
<td>9 (36%)</td>
<td>9 (36%)</td>
<td>25 (100%)</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>CPT A6 (n = 35)</td>
<td>21 (60%)</td>
<td>23 (66%)</td>
<td>35 (100%)</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>CPT B (n = 9)</td>
<td>7 (78%)</td>
<td>9 (100%)</td>
<td>9 (100%)</td>
<td>8 (89%)</td>
</tr>
</tbody>
</table>

*Of 5 pts with EOT detectable HCVRNA (4 were F3 and 1, F4), 4 achieved SVR. 1/7 patient with ascites, and 1/71 F3, suspect of lack of adherence, had a relapse. None of 6 patients with esophageal varices relapsed. One of the 6 patients with HCC discontinued treatment. RBV dose reductions were required in 5.6% of pts, one of them did not achieve SVR.
Background and Aims: Liver size may be important in prognostication in cirrhosis. The LAAR score has previously shown a relationship between liver size and survival but is hampered by subjectivity. The current study aimed to improve the existing score and to assess its relationship with liver volume, as well as assessing the accuracy and user variability of liver volume measurement when using cross-sectional imaging. Methods: A retrospective-prospective cohort study was performed on patients with cirrhosis. The censor point used was date of patient death or liver transplant (LT) from CT date. Time points were measured from the date of the CT scan to censor point or last clinic appointment. The enhanced Liverpool to Abdomen Area Ration (eLAAR) was derived using a software package (Carestream). eLAAR was calculated using the formula (Liver area (cm2)/Abdominal area (cm2) × 100. The free PAC software system OsiriX® was used to the measure the total liver volumes. The perimeter of multiple slices of the liver were traced manually on OsiriX® using the “closed polygon tool” which then created a 3d model of the liver providing the liver volume for each patient. A junior doctor initially measured liver volume on cross-sectional imaging and then this was performed again by a consultant radiologist. Results: 101 patients were identified, 66% male, median age 52 (44–60 years). The LAAR score detected progression to death/LT in our cohort at 1 year (p = 0.02) and at 5 years (p = 0.03). The intra-class correlation coefficient between 2 operators was 0.94 (95% CI 0.89–0.97). Using an optimal eLAAR cut-off of 32 eLAAR could predict death at 1 and 5 years from diagnosis, p = 0.03 (OR 2.51 (1.08–2.51) and p = 0.002 (OR 3.98 95% CI 1.5–10.4). Survival curves were constructed and the log rank test showed that eLAAR was able to predict death at 1 year (Log rank 5.3, p = 0.02) and 5 years (log-rank, p = 9.7, p = 0.002). Using 24 patients to calculate liver volume, it was shown that liver volume correlates with patient survival (Z Score 5.9282, U-Value 0, p value 0, p ≤ 0.05). There was also a positive correlation between the value of eLAAR and the volume of liver calculated (R = 0.6046) for each patient. Conclusions: The eLAAR score and liver volume calculation offers a new paradigm to identify cirrhotic patients with poor prognostic criteria on cross-sectional imaging who may benefit from liver transplantation. eLAAR correlates with liver volume and both can be used to predict survival of cirrhotic patients in this pilot study.
Background and Aims: Hepatitis C viral (HCV) infection is a global health problem affecting over 170 million people worldwide. HCV genotype 3 (GT3) infection is commonly found in Latin America (5% > 30%), Europe (20% > 40%) and Asia (30% > 45%), and affects 12% of HCV patients in the United States. Studies have shown that the combination of sofosbuvir (SOF) and daclatasvir (DCV) achieved 12-week sustained virologic response (SVR12) in 96% of HCV GT3-infected, treatment-naive patients without cirrhosis following a 12-week treatment regimen. Currently, 2 next-generation direct-acting antiviral agents (DAA), ABT-493 (identified by AbbVie and Enanta), an HCV NS3/4A protease inhibitor and ABT-530, an NS5A inhibitor, are being developed for the treatment of all 6 major HCV genotypes. In a phase 2b study (M14-868 Part 1), promising efficacy and safety results were obtained in GT3-infected patients receiving ABT-493 and ABT-530 for 12 weeks. In this phase 3 study, the efficacy and safety of ABT-493 and ABT-530 combination will be confirmed in treatment-naive non-cirrhotic HCV GT3-infected patients and directly compared to the standard-of-care SOF + DCV regimen. Results: This is a Phase 3, randomized, open-label, active-controlled, multicenter study. Patients will be randomized approximately 2:1 across 2 arms. Arm A will enroll approximately 230 HCV GT3-infected, treatment-naive patients without cirrhosis who will receive ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks. Arm B will enroll approximately 115 HCV GT3-infected, treatment-naive patients without cirrhosis who will receive SOF 400 mg + DCV 60 mg QD for 12 weeks. Patients who complete or prematurely discontinue the treatment will be followed for 24 weeks after their last dose of study drugs to evaluate efficacy and the emergence and persistence of viral variants. The first primary objective of this study is to demonstrate non-inferiority of the ABT-493/ABT-530 regimen compared to SOF + DCV by analyzing the percentage of patients achieving SVR12 following 12 weeks of treatment with ABT-493/ABT-530. Additionally, pharmacokinetics of the study drugs will be analyzed in the study.
Background and Aims: The phase 2 studies of sofosbuvir (SOF) in combination with velpatasvir (pangenotypic HCV NS5A inhibitor) ± ribavirin (RBV) assessed dose (25 mg or 100 mg VEL), treatment duration (8 or 12 weeks) and the need for RBV use. The SVR rates across all treatment groups ranged from 58% to 100%. This current study evaluated the safety and efficacy of the once-daily fixed-dose combination tablet of sofosbuvir/velpatasvir (SOF/VEL) + RBV for 24 weeks in patients from these phase 2 studies who experienced virologic failure. Methods: This was a single arm, open label study of HCV infected subjects who failed treatment in the phase 2 studies (GS-US-342-0102, GS-US-342-0109 and GS-US-337-1122). Patients received SOF/VEL (400 mg/100 mg daily) in combination with weight based RBV (1,000 or 1,200 mg daily) for 24 weeks. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12). Secondary endpoints included safety, tolerability, resistance, and additional efficacy outcomes. Results: A total of 41 subjects were enrolled and treated with SOF/VEL + RBV for 24 weeks. Overall 78% were male, 93% were white, 34% had IL28B CC genotype and 24% had compensated cirrhosis. The genotype (GT) distribution was 27% GT1, 34% GT2, and 39% GT3. 24 (59%) patients had NS5A resistance associated variants (RAVs) at baseline of which 40% had high level RAVs (>100 fold shift in EC50 for VEL). Prior treatment exposure and outcome from the phase 2 studies are described in Table 1. HCV RNA declined rapidly with 95% of subjects achieving HCV RNA declined rapidly with 95% of subjects achieving HCV RNA <LLOQ at treatment week 4. In this interim analysis, 25 of 28 (90%) patients were <LLOQ at the post treatment week 4 visit. No subject discontinued SOF/VEL due to adverse events (AEs), however 1 subject discontinued RBV for worsening cough. The most common AEs were fatigue (24%), headache (20%) and nausea (20%). One subject experienced a serious adverse event (nephrolithiasis) which was considered unrelated to study drugs. Efficacy, safety and resistance outcomes including final SVR12 results and the impact of HCV resistance mutations on outcome will be presented. Conclusions: Among patients who failed initial treatment with SOF/VEL ± RBV for 8–12 weeks, retreatment with a longer duration of SOF/VEL +RBV for 24 weeks is well tolerated and associated with rapid virologic suppression in all patients.
<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
</tbody>
</table>

**Abstract Body**

**HIGH EFFICACY OF SOFOSBUVIR/VELPATASVIR/GS-9857 WITH OR WITHOUT RIBAVIRIN FOR 12 WEEKS IN DIRECT ACTING ANTIVIRAL-EXPERIENCED PATIENTS WITH GENOTYPE 1 HCV INFECTION**
LEDIPASVIR/SOFOSBUVIR FOR 12 OR 24 WEEKS IS SAFE AND EFFECTIVE IN KIDNEY TRANSPLANT RECIPIENTS WITH CHRONIC GENOTYPE 1 OR 4 HCV INFECTION

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>GS13</td>
</tr>
</tbody>
</table>

**Abstract Body**

Background and Aims: Interferon (IFN) and ribavirin (RBV) for the treatment of chronic hepatitis C (HCV) in kidney transplant recipients is complicated by the risk of the allograft rejection and poor tolerability. We evaluated the safety and efficacy of the IFN-free, RBV-free regimen of ledipasvir/sofosbuvir (LDV/SOF) in chronic genotype (GT) 1 or 4 HCV infected kidney transplant recipients. Methods: Kidney transplant recipients with chronic GT1 or GT4 HCV infection, treatment-naïve and treatment-experienced, with or without compensated cirrhosis were randomized 1:1 at 5 sites in Europe to receive LDV/SOF (90 mg/400 mg) for 12 or 24 weeks. Randomization was stratified by HCV genotype, treatment history and presence or absence of cirrhosis. Cirrhosis was determined by liver biopsy (Metavir score = 4 or Ishak score ≥5), Fibroscan® >12.5 kPa, or Fibrotest® >0.75 and APRI >2. A pretreatment creatinine clearance <40 mL/min was an exclusionary criterion. The primary endpoint was SVR12. Results: 114 patients were randomized and treated; median age was 53, 58% were male, 94% were white, 72% carried the non-CC IL28B allele, 91% had genotype 1 infection, 69% were treatment-naïve, and 15% had compensated cirrhosis. The median eGFR was 56 mL/min (range 35–135 mL/min). All 92 patients with SVR4 data available achieved SVR4 including a patient discontinuing treatment at Week 4 due to an AE. SAEs were reported in 12 (11%) patients; 3 were assessed as treatment related: syncope, pulmonary embolism, and blood creatinine increased. The most frequent AEs were headache (19%), asthenia (13%), and fatigue (10%). Conclusions: Administration of LDV/SOF for 12 or 24 weeks in patients with chronic HCV genotype 1 or 4 patients who have undergone kidney transplant was safe and highly effective with an SVR4 rate of 100%. Treatment was well-tolerated. SVR12 data for all patients will be presented.
# HIGH RATES OF SVR12 IN ADOLESCENTS TREATED WITH THE COMBINATION OF Ledipasvir/Sofosbuvir

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
</tbody>
</table>

**Abstract Number**

**Abstract Body**
C-SWIFT RETREATMENT FINAL RESULTS: HIGHLY SUCCESSFUL RETREATMENT OF GT1-INFECTED PATIENTS WITH 12 WEEKS OF ELBASVIR/GRAZOPREVIR PLUS SOFOSBUVIR AND RIBAVIRIN AFTER FAILURE OF SHORT-DURATION ALL-ORAL THERAPY

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>SAT-148</td>
</tr>
</tbody>
</table>

Abstract Body: Background and Aims: Therapies to retreat patients who have failed prior all-oral, direct-acting antiviral therapies have not been defined. The purpose of this study was to assess a retreatment regimen for subjects who had failed therapy with elbasvir/grazoprevir (EBR/GZR, an NS5A inhibitor + potent NS3/4A protease inhibitor fixed-dose combination) + sofosbuvir (SOF). Methods: Genotype 1-infected patients who relapsed after therapy with EBR/GZR + SOF for 4, 6 or 8 weeks were offered retreatment with 12 weeks of EBR/GZR + SOF + ribavirin (RBV). The primary endpoint was the proportion of patients achieving hepatitis C virus RNA < 15 IU/mL 12 weeks after end of treatment (SVR12). Population sequencing was used to detect resistance-associated variants (RAVs) in NS3, NS5A and NS5B. Results: Twenty-five of 29 eligible patients were enrolled: 88% (22/25) with G1a infection; 20% (5/25) with cirrhosis; baseline viral load mean 6.6 log10 IU/mL (range: 4.3–7.4 log10 IU/mL). At baseline of retreatment, 80% (20/25) patients had NS5A RAVs, 52% (13/25) had an NS3 RAV and 0/25 had an NS5B RAV. NS5A variants at the following positions occurred in 16–32% of the retreatment population, M28, Q30, L31, H58 and Y93. Nine subjects had both an NS5A and NS3 RAV at baseline. Twenty-three of 25 subjects completed therapy. Two patients were lost to follow-up; one after treatment day 3 and one after treatment week 4, at which time viral load was 363 IU/mL and target not detected, respectively. SVR12 was achieved in 100% of the 23 patients who completed therapy. One patient discontinued RBV only due to pruritus. Rash, fatigue and nausea were the most frequent adverse events occurring in 8% of patients. Conclusions: 100% SVR12 was achieved with a 12-week regimen of EBR/GZR + SOF + RBV regardless of cirrhosis and high prevalence of RAVs (including two class RAVs). Final SVR24 results will be presented.
BASELINE CLINICAL AND LABORATORY PARAMETERS ASSOCIATED WITH CLINICAL BENEFITS OF SUCCESSFUL HCV TREATMENT WITH SOFOSBUVIR/VELPATASVIR IN DECOMPENSATED CIRRHOTIC PATIENTS

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-169

Abstract Body: Background and Aims: HCV treatment options remain limited in patients with decompensated cirrhosis. Treatment with sofosbuvir/velpatasvir (SOF/VEL) regimens demonstrated high efficacy rates in genotype 1–6 HCV infected patients with decompensated cirrhosis (ASTRAL-4). This analysis explores the effect of viral clearance on clinical outcomes and also attempts to identify key clinical and laboratory parameters associated with changes in MELD or CPT score in patients who achieve SVR.

Methods: In the ASTRAL-4 study, HCV infected patients with CPT-B cirrhosis were randomized 1:1:1 to receive SOF/VEL (400 mg/100 mg) daily for 12 weeks, SOF/VEL + weight based RBV for 12 weeks, or SOF/VEL for 24 weeks. Efficacy and safety data including MELD and CPT scores were assessed at baseline, on treatment and through post treatment week 24. Results: Of the 267 patients randomized and treated, the majority were male (70%), white (90%), IL28B non-CC (76%) and treatment experienced (55%). The median CPT score was 8 (range 5–10) and median MELD score of 10 (range 6–24). The overall SVR12 rates by treatment regimen were 83% (SOF/VEL 12 weeks), 94% (SOF/VEL + RBV 12 weeks) and 86% (SOF/VEL 24 weeks). Of the 234 subjects who achieved SVR12, 47% had an improvement in CPT score (range: 1−5 points) while 43% had no change from baseline to post-treatment Week 12. Decreases in CPT score were primarily due to improvements in albumin (68%) and bilirubin (36%). Among patients who had a MELD score ≥15 at baseline and achieved SVR12, 84% had an improvement in MELD (range 1–11 points); 62% improved to MELD <15. In patients with baseline MELD score ≤15, 52% had an improvement (range 1–7 points). Improvements in MELD score were largely due to decreases in total bilirubin. An exploratory analysis of baseline predictors of changes in MELD scores in patients who achieved SVR12 is shown in Table 1. Patients without clinical manifestations of portal hypertension (no vs. severe ascites, 56% vs. 17%), shunting (grade 0 vs grade 1–2 hepatic encephalopathy, 71% vs. 46%), and lower BMI (<30 vs. ≥30, 60% vs 49%) had a greater proportion with MELD score improvement. Clinical and laboratory changes at post-treatment week 24 will be presented. Conclusions: Treatment with SOF/VEL regimens had high efficacy rates in patients with decompensated cirrhosis. Patients who achieved SVR12 had a higher probability of clinical improvement if they had a higher MELD score, lower (<30) BMI or the absence of ascites and encephalopathy at the time of enrollment.
COMPARISON OF FREQUENCIES OF DRUG-DRUG INTERACTIONS BETWEEN SOFOSBUVIR/LEDIPASVIR AND
OMBITASVIR/DASABUVIR/PARITAPREVIR/RITONAVIR +/- RIBAVIRIN AMONG HIV/HCV COINFECTED PATIENTS

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-223

Abstract Body

Background and Aims: Sofosbuvir/ledipasvir (SOF/LDV) and ombitasvir/paritaprevir/dasabuvir/ritonavir ± ribavirin (OPDRr) are two options for GT1 HCV. HIV + patients are at high risk for drug interactions when new medications are added. Study objectives were: 1) compare prevalence of contraindicated drug interactions (XDDI) between SOF/LDV and OPDRr when added to patient medication profiles and 2) determine predictors of XDDIs for each regimen. Methods: A cross-sectional study was performed among patients from 3 US sites. Inclusion criteria were: 1) age ≥18 years, 2) HIV & HCV infections and 3) availability of medication list. Data extracted included: demographics, comorbidities, and most recent medication list. Primary outcome was the presence of XDDIs involving HCV therapy and patient’s home medication list after the addition of either regimen. An automated software program (Lexi-Interact) was used to define the presence of XDDIs. Only XDDIs with the highest severity rating were considered clinically significant. Results: Of the 412 subjects, mean ± standard deviation (SD) age was 54.9 ± 7.6 years. Among the 382 patients on antiretroviral therapy (ART), regimens types were non-nucleoside reverse transcriptase inhibitors (NNRTI, 38.0%), protease inhibitors (PI, 35.8%), mixed class (14.7%) and integrase strand transfer inhibitors (INSTI, 8.6%). The median (interquartile range, IQR) number of comorbidities was 7 (4–11). Patients were using a median (IQR) of 7 (4–10) non-HIV medications. Prior to the addition of SOF/LDV and OPDRr, the baseline rate of XDDIs was 20.8% overall. After addition of HCV therapy, frequencies of XDDIs were significantly lower for SOF/LDV (6.1%) compared to OPDRr (60.3%), p < 0.001. Independent predictors of SOF/LDV-XDDIs were antipsychotics (odds ratio, OR: 2.34, 95% confidence interval, CI: 1.11–4.96, p = 0.03), antiepileptics (OR: 8.96, 95% CI: 4.36–18.42, p < 0.001) and INSTIs (OR: 1.41, 95% CI: 1.13–1.77, p = 0.002). Independent predictors of OPDRr-XDDIs were use of NNRTIs (OR: 3.11, 95% CI: 2.55–3.81, p < 0.001), PIs (OR: 1.73, 95% CI: 1,43–2.09, p < 0.001) and number of non-HIV medications (OR: 1.02, 95% CI: 1.01–1.03, p = 0.02). Conclusions: Prevalence of XDDIs involving HCV therapies and other medications prescribed to HIV/HCV coinfected patients were significantly less with SOF/LDV than with OPDr. Independent predictors of SOF/LDV-XDDIs were antipsychotics, antiepileptics and INSTIs. Independent predictors of OPDRr-XDDIs were use of NNRTIs (OR: 3.11, 95% CI: 2.55–3.81, p < 0.001), PIs (OR: 1.73, 95% CI: 1.43–2.09, p < 0.001) and number of non-HIV medications (OR: 1.02, 95% CI: 1.01–1.03, p = 0.02). Conclusions: Prevalence of XDDIs involving HCV therapies and other medications prescribed to HIV/HCV coinfected patients were significantly less with SOF/LDV than with OPDr.
Background and Aims: Treatment options are limited for patients with HCV infection and advanced fibrosis or cirrhosis before or after liver transplantation. The pangenotypic combination of daclatasvir (DCV) and sofosbuvir (SOF) with ribavirin (RBV) previously demonstrated 94% SVR rates in liver transplant recipients with HCV recurrence, and 83% in patients with advanced cirrhosis. We report interim findings from a US DCV expanded access protocol in patients with decompensated cirrhosis or post-liver transplant recurrence with advanced fibrosis/cirrhosis. Methods: This multi-centre, expanded access protocol, provided open-label DCV for use in combination with SOF, ±RBV (at the physician’s discretion) for 24 weeks, in patients with genotype (GT) 1–6 in 2 cohorts: (1) decompensated (Child-Pugh C) cirrhosis, and (2) F3 fibrosis, cirrhosis, or fibrosing cholestatic hepatitis after liver transplantation. The HCV TARGET consortium was utilized for treatment and data collection. Results: Of 74 patients treated, 65 received DCV + SOF and 9 DCV + SOF + RBV. Patients were mostly male (80%) and white (88%), with HCV GT 1 (61%) or GT 3 (34%); 43% had failed prior IFN-based regimens, 80% had received a liver transplant, 80% had evidence of prior decompensation, and cirrhosis was present in 84%. At baseline, median (range) platelets were 116 (27–420) × 10³ cells/μL, albumin 3.3 (1.7–4.7) g/dL, total bilirubin 1.1 (0.3–15.3) mg/dL, and creatinine clearance was 84.8 (35.4–258.7) mL/min. MELD was ≥10 in 59% of patients (24/41) with available scores. Of 41 patients with available data at posttreatment week 12, 35 (85%) achieved SVR. Among the 32 GT 1 patients with available outcomes, 29 achieved SVR (91%), 1 patient relapsed, and 2 were lost to follow-up. Among GT 2 patients, 2 patients achieved SVR and 2 were lost to follow-up. In the 7 GT 3 patients, 6 achieved SVR (86%) and 1 patient had viral breakthrough. Adverse events occurring in ≥10% of patients were fatigue, headache, nausea, diarrhoea, abdominal pain, asthenia, insomnia and vomiting. Serious adverse events of interest included hepatic failure (n = 1) and renal failure (n = 4); 4 patients died (cardiac arrest, hepatic failure, hepatorenal syndrome, sepsis); 10 patients discontinued treatment for adverse events. Conclusions: DCV + SOF ± RBV for 24 weeks was efficacious and welltolerated in patients with decompensated cirrhosis, or severe recurrent post-transplant hepatitis C, receiving this regimen through compassionate use.
### Abstract

**Background and Aims:** Sofosbuvir-ledipasvir (SOF/LDV) is a highly effective and safe hepatitis C virus (HCV) treatment regimen. The aim of this study is to evaluate if patients with pre-existing renal dysfunction are at higher risk for worsening kidney disease during treatment. Methods: This is a retrospective cohort study of patients treated with SOF/LDV. Creatinine and CrCl were collected at baseline, 4 weeks into therapy, end of therapy, 4 weeks after therapy, and 12 weeks after therapy. Abnormal baseline renal function was defined as CrCl <60. Patients with lower CrCl at completion of therapy compared to baseline were considered to have worsening renal function while on HCV treatment. All statistical analysis was performed by SAS 9.4. Results: Ninety patients treated with SOF/LDV had complete data and included in analysis. 15 patients were treated for 8 weeks, 67 patients with 12 weeks, and 8 patients with 24 weeks. 17 patients had abnormal baseline renal function, with 42% having worsening CrCl while on treatment. Univariate analysis demonstrated baseline CrCl <60 to be significantly associated with worsening renal function (p = 0.016). Baseline CrCl <60 remained significantly associated with worsening renal function (p = 0.04) in multivariate logistic regression controlling for age, duration of treatment and presence of advanced fibrosis. Changes in renal function after completion of therapy will also be reported. Conclusions: This was a retrospective study of the effect of SOF/LDV on CrCl during treatment for HCV. Patients with an abnormal baseline CrCl were more likely than those with normal CrCl to have worsening kidney function while on HCV treatment. Based on this data, it worth exercising caution when using SOF/LDV with patients with pre-existing renal dysfunction. Future studies are needed with larger patient cohorts to verify this finding.

### Table

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>SAT-262</td>
</tr>
<tr>
<td>Abstract Body</td>
<td>Background and Aims: Sofosbuvir-ledipasvir (SOF/LDV) is a highly effective and safe hepatitis C virus (HCV) treatment regimen. The aim of this study is to evaluate if patients with pre-existing renal dysfunction are at higher risk for worsening kidney disease during treatment. Methods: This is a retrospective cohort study of patients treated with SOF/LDV. Creatinine and CrCl were collected at baseline, 4 weeks into therapy, end of therapy, 4 weeks after therapy, and 12 weeks after therapy. Abnormal baseline renal function was defined as CrCl &lt;60. Patients with lower CrCl at completion of therapy compared to baseline were considered to have worsening renal function while on HCV treatment. All statistical analysis was performed by SAS 9.4. Results: Ninety patients treated with SOF/LDV had complete data and included in analysis. 15 patients were treated for 8 weeks, 67 patients with 12 weeks, and 8 patients with 24 weeks. 17 patients had abnormal baseline renal function, with 42% having worsening CrCl while on treatment. Univariate analysis demonstrated baseline CrCl &lt;60 to be significantly associated with worsening renal function (p = 0.016). Baseline CrCl &lt;60 remained significantly associated with worsening renal function (p = 0.04) in multivariate logistic regression controlling for age, duration of treatment and presence of advanced fibrosis. Changes in renal function after completion of therapy will also be reported. Conclusions: This was a retrospective study of the effect of SOF/LDV on CrCl during treatment for HCV. Patients with an abnormal baseline CrCl were more likely than those with normal CrCl to have worsening kidney function while on HCV treatment. Based on this data, it worth exercising caution when using SOF/LDV with patients with pre-existing renal dysfunction. Future studies are needed with larger patient cohorts to verify this finding.</td>
</tr>
</tbody>
</table>
Background and Aims: Ledipasvir/sofosbuvir (LDV/SOF) has yielded SVR12 rates of over 95% in post-transplant, genotype 1 non-cirrhotic, patients (Manns M. et al. SOLAR 2 trial. J. Hepatology 2015; 62(1) supplemental). Given the remarkable efficacy in clinical trials we aim to understand real-world outcomes across a heterogeneous posttransplant population. The purpose of this study is to examine a real-world population to assess SVR12 rates in post-transplant genotype 1 HCV patients who were treated with LDV/SOF ± RBV for 8, 12, or 24 weeks. Methods: Data were collected from providers and specialty pharmacies through Trio Health’s Innervation Platform, a cloud-based disease management program. All post-transplant genotype 1 HCV patients who initiated treatment with LDV/SOF+/−RBV, between Oct 2014 and Mar 2015 were included in the analysis (n = 57). Data collected includes 25%(14/47) treated in a community site, 77% (44/57) males, 17% (9/53) African Americans, 68% (36/53) genotype 1a, 54% (31/57) HCV treatment-experienced, 32% (18/56) with cirrhosis, and 29% (16/56) with a baseline viral RNA of 6MMIU/ml or greater. 4% (2/57) of patients were treated with 8 weeks, 79% (45/57) on 12 weeks, and 17% (10/57) on 24 weeks of LDV/SOF+/−RBV. Of the 17 cirrhotic patients, 3 had decompensated cirrhosis. 2 achieved SVR and 1 patient failed out of this group. Results: Overall SVR12 rate from this heterogeneous population was 93% (53/57). Of the 4 patients that did not achieve SVR12, 1 patient discontinued, 2 were lost to follow-up, and only 1 patients was a virological failure. SVR rates did not differ significantly between genotypes 1a and 1b (both groups seeing a 94% SVR12 rate). Varying SVR12 rates were observed in prior treatment status (87% in treatment-experienced versus 100% in treatment-naïve), presence or absence of cirrhosis (83% in cirrhotic patients versus 97% in noncirrhotics), platelets (86% in with platelets <100 k/mL versus 96% with platelets of 100k+/mL), and duration of therapy (100%, 98%, 70% in 8, 12, 24 weeks of therapy respectively). Conclusions: Overall SVR12 in real-world post-transplant genotype 1 HCV patients is 93% across regimens and various patient characteristics. SVR rates did not differ significantly genotypes 1a and 1b, but differences in SVR12 rates were observed in prior treatment status, presence or absence of cirrhosis, platelets, and duration of therapy.
Background and Aims: The all-oral, pan-genotypic combination of daclatasvir + sofosbuvir ± ribavirin demonstrated high sustained virologic response rates (SVR12) in phase 3 studies of different patient groups with chronic HCV infection. We report efficacy and safety results from a large European compassionate use program that provided daclatasvir + sofosbuvir ± ribavirin therapy to patients with chronic HCV infection and severe liver disease. Methods: Eligible patients were adults with chronic HCV infection at a high risk of hepatic decompensation or death within 12 months if left untreated, or urgent need of viral clearance due to extrahepatic manifestations or comorbidities, and with no available treatment options. Patients received daclatasvir 60 mg + sofosbuvir 400 mg once daily for 24 weeks; ribavirin addition or reduced treatment duration was the physician’s choice. The primary efficacy outcome was sustained virologic response at posttreatment Week 12 (SVR12). Results: 485 patients were enrolled; efficacy data were available for 436. Most patients were male (66%), white (93%), and HCV treatment experienced (70%). HCV genotype (GT) distribution was GT1a 33%, GT1b 36%, GT1 subtype other/unknown 4%, GT3 21%, GT4 4%, other GT 2%; mean HCV RNA was 5.5 log10 IU/mL. Cirrhosis was confirmed in 388 (80%) patients, of whom 165 (43%) were Child-Pugh class B or C; 37 (10%) had MELD scores >15. 87 patients (18%) were liver transplant recipients and 55 (11%) were HIV/HCV coinfected. SVR12 was achieved by 394/436 (90%) patients (Table 1). There were 13 relapses and 1 on-treatment virologic failure. SVR12 rates were similar with/without ribavirin and comparable across HCV GT, presence of cirrhosis, liver transplant status, HIV coinfection, and other baseline characteristics. There were 28 deaths over treatment or follow-up (none considered treatment-related), 91 experienced serious adverse events (11 considered treatment-related), and 38 discontinued treatment or died due to adverse events (10 treatmentrelated). Most deaths and serious adverse events were directly or indirectly associated with advanced liver disease. Adverse events (any grade) occurring in ≥5% of patients were fatigue, anaemia, headache, nausea, and diarrhoea. Conclusions: The all-oral regimen of daclatasvir + sofosbuvir ± ribavirin was highly effective and well tolerated in this large European real-world cohort of patients with advanced liver disease.

DACLATASVIR PLUS SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN FOR TREATMENT OF CHRONIC HCV INFECTION IN PATIENTS WITH ADVANCED LIVER DISEASE: RESULTS OF A EUROPEAN COMPASSIONATE USE PROGRAM
Background and Aims: An estimated 185 million individuals worldwide are infected with Hepatitis C (HCV). The introduction of ledipasvir/sofosbuvir (LDV/SOF) for the treatment of HCV provides an interferon-free treatment regimen with treatment durations ranging from 8 to 24 weeks. This study assessed expected and observed treatment duration and evaluated factors associated with adherence, which may help providers identify patients at risk for adherencerelated treatment failure. Methods: Patients with HCV treated with LDV/SOF between 11/2014 and 6/2015 and enrolled in large US health plans were identified. Patients had continuous enrollment with medical and pharmacy coverage for at least 12 months pre-treatment through treatment completion. Expected treatment duration was determined by whether patients were treatment naïve (during ≥1 year pretreatment) or treatment experienced, were diagnosed with cirrhosis, HCV genotype, and HCV RNA. HCV treatment and comorbidities were identified with diagnosis and procedure codes in medical claims. Multivariate logistic regression model was used to identify factors associated with adherence, controlling for patient demographics and comorbidities. Results: The study included 1,518 LDV/SOF patients, including 35 with LDV/SOF+RBV. Most patients were male (64.0%) with mean age 59.8 years and slightly more (52.0%) enrolled in commercial insurance than in Medicare Advantage. Most patients (84.8%) were classified as treatment naïve. 55.8% of patients had pre-treatment medical history for ≥3 years. Cirrhosis or end stage liver disease was present in 46.8%. Patients were treated for 24 weeks (1.8%). Among patients with a probable 8-week treatment regimen (n = 176), half (50.0%) were treated longer. Most patients (99.6%) with expected 12-week treatment durations (n = 714) completed on time. Patients who were treatment experienced had lower odds of completing the expected number of weeks of treatment (odds ratio = 0.525, p < 0.01). Diagnosis of cirrhosis was not statistical predictors of adherence (p = 0.06), nor were other demographics and comorbidities. Conclusions: Within the observed sample of a US insured population, half of patients with HCV who were treated with an 8-week LDV/SOF regimen were treated longer while most patients with a 12-week regimen completed on time. Controlling for other factors, prior HCV treatment was associated with lower likelihood of completing the expected amount of treatment.
Background and Aims: Management of HCV among kidney transplanted (KT) patients remains a challenge, due to drug interactions and/or frequent renal impairment that limits the use of RBV and certain DAAS, such as sofosbuvir (SOF). Therefore, there is still limited information on “real life” data on SOF-based treatment in this population. Methods: To describe the safety and efficacy of 12 cycles of IFN/RBV-free, SOF-based therapies in 11 KT patients with chronic hepatitis C. Results: Median time from KT to therapy was 212w (35–1861). 82% patients (N = 9) were on triple immunosuppressive therapy with calcineurin inhibitors (tacrolimus in all but one on cyclosporine) plus micophenolate plus steroids. Median age 53 y (48–68), male 82% (N = 9), 27% HIV-coinfected (N = 3). IL28B genotype was available in 6 (54%; 4CC and 2 CT). 73% were naïve to anti-HCV therapy (n = 8); 54% showed histological severity (n = 6): cirrhosis in 5 (only one with prior decompensation), fibrosing cholestatic hepatitis (FCH) in one HCV-G1b KT female 57 days after undergoing liver transplantation. All subjects received IFN/RBV-free, full-dose SOF-based therapy: 64% SOF/LDV (N = 7, 12w in 6), 27% SOF/DCV (N = 3, all 24w); 9% SOF/SMV (N = 1, 24w). Median baseline eGFR (CKD-EPI) was 39 mL/min (range 23–102; 73% below 50 mL/min, and below 30 mL/min in 2). Median baseline HCV-RNA was 6.4 log10 IU/ mL (4.38–8.23). All but one subjects completed the scheduled regimen, with an overall rate of SVR of 91%, 100% among patients receiving 12w of SOF/LDV. There was only a premature discontinuation, due to virological failure, in the kidney/liver transplanted female with FCH and the highest baseline HCV-RNA, that did not reach negative HCV-RNA during SOF/DCV; after 98 days RBV was added, and after she also received SMV, with SVR after an overall duration of SOF-based therapy of 24w. SOF did not significantly worsen eGFR, and all subjects maintained full doses during therapy. There was only one admission due to E coli urinary tract infection, successfully managed with antibiotics. Mild adjustments in immunosuppressive therapy were performed in 36% (n = 4). Conclusions: IFN/RBV-free, full dose SFB-based therapy was safe and highly effective among KT patients, with RVS in 91% (100% among subjects after 12w of SOF/LDV). There were no adverse events or impairment in eGFR despite a high prevalence or baseline renal impairment.
Background and Aims: In untreated HCV-infected patients who undergo liver transplantation, recurrence of HCV infection is universal and is associated with poorer graft and patient survival compared with patients undergoing liver transplantation for other causes. The aim of this analysis is to evaluate outcomes in patients who underwent liver transplant after initiating treatment with ledipasvir (LDV)/sofosbuvir (SOF) + ribavirin (RBV) in the SOLAR-1 and SOLAR-2 trials. Methods: We combined data from the SOLAR-1 and SOLAR-2 studies, in which 7 groups of patients with HCV genotype (GT) 1 or 4, from US, Europe, Canada, Australia and New Zealand, were randomized to receive 12 or 24 weeks of LDV/SOF + RBV: patients without a transplant with 1) Child-Pugh-Turcotte (CPT) B or 2) CPT C cirrhosis; or transplanted patients with 3) no cirrhosis (F0 to F3), 4) CPT A, 5) CPT B or, 6) CPT C cirrhosis, or 7) fibrosing cholestatic hepatitis. Results: Seventeen patients underwent liver transplantation during the study. For all but one patient, this was the first liver transplant. In terms of disease characteristics, 11 of the 17 were GT1a, 5 were GT1b, and 1 was GT4. Six were CPT B at screening (5 Group 1, 1 Group 5) and 11 were CPT C (Group 2). Median baseline MELD score was 17 (range 7–23), with the majority (11/17) having scores ≥15. Seven patients underwent transplant prior to completing their full course of treatment. All patients were HCV RNA < LLOQ at the time of liver transplant. All but one patient (94%, 16/17) maintained virologic response 12 weeks after transplant (pTVR12). All patients who achieved pTVR12 received at least 11 weeks of LDV/SOF + RBV. The one patient who did not achieve pTVR12 discontinued study drug on day 21 and underwent liver transplant the following day. His baseline MELD score was 16 but the value increased to 40 by Day 11 and was 36 at Day 18. CPT score was 10 at baseline and increased to 13 from Day 11–18. The subject had HCV RNA < LLOQ at post-transplant Week 2 but died 15 days post-transplant due to multi-organ failure and septic shock. Conclusions: Few patients with decompensated cirrhosis treated in the SOLAR studies underwent liver transplantation after initiating LDV/SOF + RBV therapy. For the 17 who did undergo transplant, 94% achieved pTVR12. The data suggest that 11 weeks of treatment prior to transplantation can prevent reinfection of the graft. Future studies are needed to assess the optimal timing and length of treatment in the peri-transplant setting.
**DACLATASVIR PLUS SOFOSBUVIR PLUS RIBAVIRIN FOR 12 OR 16 WEEKS IN TREATMENT-EXPERIENCED PATIENTS WITH HCV GENOTYPE 3 INFECTION AND ADVANCED FIBROSIS OR CIRRHOSIS**

| Company | Gilead |
| Drug | Sofosbuvir |
| Abstract Number | SAT-129 |

**Abstract Body**

Background and Aims: Patients with HCV genotype 3 infection are a challenging population in urgent need of optimally effective therapies. The phase 3 ALLY-3+ study evaluated 12 and 16 weeks of daclatasvir + sofosbuvir + ribavirin in patients with HCV GT 3 infection and advanced fibrosis or cirrhosis. Sustained virologic response at posttreatment Week 12 (SVR12) was achieved by 100% of patients with advanced fibrosis and 86% of patients with cirrhosis. Here, we present the results of the treatment-experienced population.

Methods: Treatment-experienced patients (N = 37) received openlabel daclatasvir 60 mg + sofosbuvir 400 mg (both once daily) + weight-based ribavirin (1,200 or 1,000 mg/day) for 12 (n = 18) or 16 (n = 19) weeks. Advanced fibrosis or cirrhosis was determined by liver biopsy, FibroScan (advanced fibrosis: ≥9.6 – 2. This subanalysis provides further details of efficacy and safety outcomes in these patients.

Results: Treatment-experienced patients were predominantly male (78%), white (97%) and cirrhotic (81%); 60% had baseline HCV RNA ≥6,000,000 IU/mL and 59% had non-CC IL28B genotypes. Patients had previously received interferon- (n = 31; 15 had prior relapse) or sofosbuvir-based (+ribavirin, n = 5; + interferon + ribavirin, n = 1; all had prior relapse) regimens. SVR12 was achieved by 89% of patients overall (12-week arm: 89%; 16-week arm: 90%), 100% of patients with advanced fibrosis (n = 7/7) and 87% of patients with cirrhosis (n = 26/30). SVR12 was also achieved by 96% of patients with baseline HCV RNA ≥6,000,000 IU/mL (n = 21/22) and 100% of patients with baseline NS5A (A30, L31 and Y93) polymorphisms (n = 5/5). Four patients failed treatment (relapse, n = 3; unrelated death, n = 1). There were no adverse events leading to study discontinuation. Serious and grade 3/4 adverse events each occurred in 11% of patients overall. Grade 3/4 laboratory abnormalities were uncommon (haemoglobin, n = 1; total bilirubin, n = 2). The most frequent adverse events overall (any grade) were insomnia (27%), fatigue (27%) and headache (24%). Conclusions: Daclatasvir + sofosbuvir + ribavirin for 12 or 16 weeks is highly efficacious in patients with HCV GT 3 infection and advanced fibrosis (SVR12, 100%) or cirrhosis (SVR12, 87%) who have failed previous interferon- or sofosbuvir-based therapies. This regimen is also safe and well tolerated.
EFFECTIVENESS AND SAFETY OF SOFOSBUVIR AND RIBAVIRIN FOR ELDERLY PATIENTS WITH HCV GENOTYPE 2 INFECTION

Company | Gilead
Drug     | Sofosbuvir
Abstract Number | SAT-140

Abstract Body

Background and Aims: The current first-line treatment option for HCV genotype 2 is the interferon-free combination of sofosbuvir and ribavirin, however, little data on elderly and cirrhotic patients can be found. The aim of this study was to evaluate the efficacy and safety of sofosbuvir and ribavirin for elderly patients with HCV genotype 2 in real-world clinical practice. Methods: This prospective, multicenter study consisted of 338 Japanese HCV genotype 2 patients (median age 63, treatment-naïve 220 and -experienced 118), including 103 (30.5%) aged ≥70 and 63 (18.6%) with cirrhosis. All patients were treated with sofosbuvir (400mg, once daily) and ribavirin (weight-based dosing) for 12 weeks. HCV RNA was measured by COBAS AmpliPrep/COBAS TaqMan HCV Test v2.0. Results: All patients will have completed treatment by the end of November 2015, therefore, we here present the currently available data for sustained virological response at 12 weeks after the end of treatment (SVR12) for 107 patients. The overall SVR12 rate was 92.5% (99/107), similar to the rates of patients aged ≥70 (90.3%, 60/62) and treatment-experienced patients (88.9%, 40/45). However, the 82.6% (19/23) rate of SVR12 for cirrhotic patients was slightly lower than the 95.2% for non-cirrhotic patients (80/84) (p = 0.06). Rapid virological response (HCV RNA undetectable at week 4) was not associated with SVR12 (RVR 94.2% [81/86] and non-RVR 85.7% [18/21]). Ribavirin dosage reduction was required for 13.3% of the patients due to anemia, especially for patients aged ≥70 (24.2%), however, this did not result in treatment failure. Only three patients (0.9%) discontinued treatment due to adverse effects. The most common adverse effect (13.2%) was anemia (hemoglobin <10.0g/dL), but the rate of severe anemia (<8.5 g/dL) was only 1.9%. Conclusions: Sofosbuvir and ribavirin for HCV genotype 2 was effective and well tolerated by patients aged ≥70. The data of all 338 patients and a multivariable regression analysis for predictors of SVR12 will be available for presentation at the congress.
Company: Gilead
Drug: Sofosbuvir

Abstract Number: SAT-149

Background and Aims: Treatment-experienced genotype 1 (GT1) HCV-infected patients with HIV co-infection are often considered as difficult-to-treat patients. The recent ION-4 study evaluated the single tablet regimen of 12 weeks ledipasvir/sofosbuvir (LDV/SOF) for HCV in HIV co-infected patients. However in this study, few patients were previously treated for HCV and have received NS3/4A protease inhibitors (PIs). The ANRS HC31 SOFTRIH study assessed the efficacy and safety of LDV/SOF in HCV NS3/4A protease inhibitor (PI)-experienced GT1 patients with HIV co-infection. Methods: We enrolled HCV GT1 HIV co-infected patients on stable antiretroviral (ARV) regimens, who had previously failed NS3/4A PI plus pegylated interferon-ribavirin triple therapy or stopped prematurely their treatment for intolerance. All patients received LDV/SOF (90 mg/400 mg) once daily for 12 weeks or 24 weeks in case of cirrhosis. Patients could receive the following ARVs: tenofovir, emtricitabine, lamivudine, raltegravir, efavirenz, rilpivirine, enfuvirtide. The primary and secondary efficacy endpoints were sustained virological response 12, 4 and 24 weeks after treatment discontinuation (SVR12, SVR4 and SVR24) respectively. Safety evaluations included adverse events (AE) and standard laboratory parameters monitoring including CD4 cell count, HIV-1 RNA levels and renal function. Results: 68 patients were enrolled in the study (Table). All patients had HIV RNA <80 copies/mL and median CD4 count was 629 cells/μL. Sixty five patients were evaluable for virological efficacy. Sixty two patients (95.4%) reached SVR4 (1 patient not evaluable at this timepoint; 2 patients with positive HCV RNA but below the lower limit of quantification), 65 patients (100%) obtained SVR12 and 58/58 patients with data available obtained SVR24. The 3 patients not evaluable for virological efficacy obtained SVR. AEs occurring in ≥10% of patients were fatigue (19.1%), high blood pressure (17.6%) and headache (11.8%) with no case of bradycardia. Serum creatinine level was not modified during the treatment period. In contrast mild proteinuria (47.1%), hypophosphatemia (30.9%), blood bicarbonate decreased (23.5%), hypokalemia (10.3%) were observed. No patient discontinued study drug due to an AE. Two patients had confirmed HIV virologic rebound. Conclusions: Considering the limited number of reports in this context, this study brings additional evidence of efficacy and safety of LDV/SOF for PI-experienced HIV co-infected patients including subjects with cirrhosis.
Background and Aims: HCV genotype-4 (G4) comprises 90% of HCV infections in Egypt. Recent studies with DAAs have often shown suboptimal rates of sustained virologic response (SVR) in cirrhotic patients. We report a Phase 3 trial of ravidasvir (RDV), a pangenotypic HCV NS5A inhibitor, plus sofosbuvir (SOF), a nucleotide HCV inhibitor, in 300 Egyptian patients (43% with cirrhosis).

Methods: Patients were 18–65 yr with HCV-G4 infection, HCV RNA >4 log10 IU/mL, without decompensated cirrhosis or other liver disease. Three patient groups were enrolled: interferon (IFN)-naïve non-cirrhotic and cirrhotic, by Fibroscan & FIB-4 score (Group 1); IFN-experienced non-cirrhotic (Group 2); and IFN-experienced cirrhotic (Group 3). Groups 1 and 2 were treated QD with RDV 200 mg + SOF 400 mg for 12 wk, randomized 1:1 to added RBV or no RBV. Group 3 received RDV + SOF + RBV, randomized 1:1 to 12 vs. 16 wk treatment. The primary endpoint is SVR12, defined as non-detectable HCV RNA (<12 IU/mL) by the Abbott Real-Time™ PCR assay at 12 wk posttreatment. Results: 300 patients were enrolled (150 in Group 1, 80 in Group 2, and 70 in Group 3); 170 were non-cirrhotic and 130 (43%) were Childs A cirrhotics. At the time of this abstract all patients have completed treatment-period evaluations, and only 31/300 have not yet completed their SVR12 evaluation. Treatment has been well tolerated, with 1 serious adverse event possibly related to treatment (transient bradycardia). HCV RNA declined rapidly and was undetectable by Wk 8 in all patients. For the 264 patients who have reached their SVR12 evaluation point, 164/164 (100%) noncirrhotic patients and 94/100 (94%) cirrhotic patients achieved SVR12. There have been no viral breakthroughs. All 6 treatment failures have been post-treatment relapses in cirrhotics receiving 12 wk treatment (1 had only 8 wk). Five patients discontinued unrelated to study treatment. Conclusions: Overall per protocol, 98% of 264 patients achieved SVR12 with SOF + RDV +/- RBV treatment, with SVR12 in all noncirrhotic patients and failures limited to 6 relapses in cirrhotic patients. RBV did not improve responses in non-cirrhotics or IFN-naïve cirrhotics. All (100%) 20 patients in Group 3 cirrhotics treated for 16 wk have achieved SVR12 (data pending on another 15), suggesting that 16 wk treatment may be sufficient for optimizing viral clearance in IFN-experienced G4 cirrhotics, the most refractory patients. Final study data will be available at the Congress.
Background and Aims: Controlled trials of direct acting antiviral therapy for Hepatitis C Virus show impressive sustained virologic response rates, but large single-center data of sofosbuvir plus ledipasvir are lacking. To study the characteristics and outcomes in a large single-center cohort receiving sofosbuvir/ledipasvir. Methods: All patients who began sofosbuvir/ledipasvir at our center from 10/2014 to 8/2015 were identified. Charts were reviewed for demographic and clinical variables and treatment response. Sustained virologic response rates at 12 weeks after therapy were compared between subcohorts. Predictors of sustained virologic response were evaluated with logistic regression. Results: 337 patients began sofosbuvir/ledipasvir during the study period. The cohort was 61% male, 56% white, 41% black, 72% genotype 1a, 21% genotype 1b, 1% genotype 3, 2% genotype 4, 53% treatment naïve, and 53% cirrhotic, of whom 20% had ascites, 27% had hepatic encephalopathy, and 39% had gastroesophageal varices. Mean (standard deviation) age was 57.7 (8.8). Median (interquartile range) Model for End-Stage Liver Disease and Child-Pugh scores of the cirrhotics were 9 (8–13) and 6 (5–7), respectively. Of the 337 patients, 304 have reached treatment endpoints, and 215 have sustained virologic response data to date. The sustained virologic response rate was 94% overall, 95% for genotype 1/4, and 33% for genotype 3 (1 of 3 genotype 3 patients; genotype 1/4 vs genotype 3 p = 0.010). The rate was 99% for non-cirrhotics and 89% for cirrhotics (p = 0.001), inwhom the rate was 93% for Child-Pugh < 7 and 83% for Child-Pugh ≥ 7 (p = 0.131). In univariate logistic regression, ribavirin use, genotype 1/4 vs 3, and cirrhosis were significant predictors of sustained virologic response (p = 0.010, 0.005, and 0.013, respectively). Among cirrhotics, ascites, varices, hepatic encephalopathy, Child-Pugh score, and Model for End-Stage Liver Disease scorewere not predictive. In multivariable regression with genotype 1/4 vs 3, ribavirin use, and cirrhosis, only cirrhosis was a significant predictor of sustained virologic response (OR 0.09, 95%CI 0.01–0.70, p = 0.021). Conclusions: In a large, single-center experience of sofosbuvir/ ledipasvir, the sustained virologic response rate was excellent at 94%, though cirrhosis was a significant negative predictor with a rate of 89%. Sustained virologic response in genotype 3 patients was expectedly poor, and sofosbuvir/ledipasvir is not currently recommended in this subgroup.
LEDIPASVIR/SOFOSBUVIR WITH RIBAVIRIN FOR 12 WEEKS IS EFFECTIVE AND SAFE IN TREATMENT-NAÏVE GENOTYPE-3 HEPATITIS C-INFECTED PATIENTS IN CANADA

**Company**
Gilead

**Drug**
Sofosbuvir

**Abstract Number**
SAT-183

**Abstract Body**

**Background and Aims:** Interferon-free regimens have demonstrated lower response rates in genotype (GT) 3 HCV-infected patients as compared to GT1 patients. Ledipasvir/sofosbuvir (LDV/SOF) with ribavirin (RBV) for 12 weeks resulted in a 100% SVR12 rate among treatment-naïve GT3 patients with and without cirrhosis in a single center Phase 2 trial. In this study, we evaluated the safety, tolerability and efficacy of LDV/SOF + RBV for 12 weeks in GT3 patients at 15 sites in Canada. Methods: Treatment-naïve GT3 HCV-infected patients with or without compensated cirrhosis received open-label LDV/SOF+RBV for 12 weeks. The primary endpoint was SVR12. Secondary endpoints included safety, tolerability, viral resistance, and additional efficacy outcomes. Results: 111 patients were randomized and treated: 61% male, 70% white, 23% Asian, 62% carried the non-CC IL28B allele, and 34% had compensated cirrhosis. Overall, the SVR4 rate was 92% (102/111). Virologic outcomes are shown in the Table 1. One patient (10% of patients were fatigue, headache, nausea, insomnia, dizziness, diarrhea and irritability. Four patients had serious AEs, none was related to treatment. Fourteen (14%) patients experienced grade 3 or 4 laboratory abnormalities, the majority of which were consistent with RBV therapy. Conclusions: LDV/SOF + RBV for 12 weeks in treatment-naïve patients with chronic HCV GT 3 infection led to high SVR4 rates. Treatment was safe and well-tolerated; the profile was consistent with that observed in the LDV/SOF + RBV groups in the Phase 3 studies. Complete SVR12 data will be presented.

<table>
<thead>
<tr>
<th>Table 1: Virologic outcome of treatment-naïve GT3 HCV-infected patients treated with LDV/SOF + RBV for 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF + RBV for 12 weeks</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>No cirrhosis (n=73)</td>
</tr>
<tr>
<td>SVR4, n(%)</td>
</tr>
<tr>
<td>On-treatment failure, n(%)</td>
</tr>
<tr>
<td>Relapse, n(%)</td>
</tr>
<tr>
<td>Other, n(%)</td>
</tr>
</tbody>
</table>

SVR, sustained virologic response.
Background and Aims: HCV-infected patients with decompensated cirrhosis are at a high risk of death and currently have limited treatment options. New all-oral, IFN-free regimens can achieve high rates of sustained virologic response in patients with severe liver disease, potentially allowing for recovery of liver function, or prevention of graft reinfection in transplant-listed patients. Here we report a detailed subanalysis of HCV-infected patients with decompensated cirrhosis treated with a combination of daclatasvir plus sofosbuvir ± ribavirin in a European compassionate use program (CUP). Methods: This multicenter CUP, opened in 5 European countries, enrolled adult patients with chronic HCV infection who were at high risk of hepatic decompensation or death within 12 months if left untreated, and who had no available treatment options. Patients received daclatasvir 60 mg + sofosbuvir 400 mg once daily for 24 weeks; shorter duration of treatment or ribavirin use was at the physician’s discretion. The primary efficacy outcome was sustained virologic response at posttreatment Week 12 (SVR12) by modified intention-to-treat analysis. Results: 165 patients with decompensated cirrhosis were enrolled, including 143 Child-Pugh class B and 22 class C; efficacy data were available for 147. The majority of patients were male (61%), white (90%), with a median age of 56 years (range, 28–85). Most patients were infected with HCV genotype (GT) 1 (n = 108) or GT3 (n = 45); 110 (67%) were treatment-experienced, 16 (10%) were post-liver transplant, and 33 (20%) had MELD scores >15. SVR12 was achieved by 108 of 127 patients (85%) who were Child-Pugh class B and 15 of 20 (75%) who were Child-Pugh class C (Table). One patient experienced virologic breakthrough and 5 patients relapsed posttreatment; all 6 were Child-Pugh class B without liver transplants. Forty-six patients (28%) experienced at least one serious adverse event; 6 patients had at least one treatment-related serious adverse event. Adverse events led to treatment discontinuation in 22 patients (13%); 4 were treatment related. 9 deaths occurred on treatment; none was treatment related. Conclusions: In this CUP subanalysis, daclatasvir plus sofosbuvir ± ribavirin led to high SVR12 rates in HCV-infected patients with decompensated cirrhosis, including liver transplant recipients; use of ribavirin did not affect efficacy outcomes. Daclatasvir plus sofosbuvir ± ribavirin therapy was well tolerated.
Background and Aims: Patients with hereditary bleeding disorders have been included in Phase 2 and 3 clinical trials of sofosbuvir (SOF) and ledipasvir/sofosbuvir (LDV/SOF) as well as in a dedicated study (n = 120) in this patient population. This integrated analysis evaluates the safety and efficacy of SOF-based regimens in HCV-infected patients with hereditary bleeding disorders. Methods: HCV-infected patients with a medical history of a hereditary bleeding disorder who participated in a SOF or LDV/SOF Phase 2 or 3 study were included in this pooled analysis. Medical history term(s) used to identify patients with bleeding disorders included variations of Hemophilia A or B, Von Willebrand’s Disease, Factor Deficiencies, or conditions associated with hemophilia such as hemophilic arthropathy. Results: A total of 184 patients (74% GT1, 9% GT2, 14% GT3, and 1% GT4) with bleeding disorders were identified across 14 studies. The majority were male (93%), Caucasian (81%), IL28B non-CC (69%), and without cirrhosis (72%). Hemophilia A (65%) and B (25%) were the most common bleeding disorders. SVR12 results are shown in the Table by treatment regimen and genotype. The most frequently reported adverse events (>10%) were headache, fatigue, and diarrhea; majority were mild or moderate in severity. One patient (1 patient. Grade 3 or 4 laboratory abnormalities were infrequent with anemia and hyperbilirubinemia the most frequent Grade 3 laboratory abnormality consistent with RBV administration. Conclusions: SOF + RBV and LDV/SOF ± RBV led to high rates of SVR in genotype 1–4 HCV infected patients with bleeding disorders. SOF-based regimens were safe and well tolerated with no new toxicity specific to patients with bleeding disorders emerging.
ALL-ORAL TREATMENT WITH DACLATASVIR PLUS SOFOSBUVIR ± RIBAVIRIN IN HCV GENOTYPE 3-INFECTED PATIENTS WITH ADVANCED FIBROSIS OR CIRRHOSIS: AN ANALYSIS OF ALLY-3 AND ALLY-3+

Company: Gilead
Drug: Sofosbuvir

Abstract Number: SAT-199

Abstract Body: Background and Aims: HCV genotype 3-infected patients with advanced liver disease are a challenging population in urgent need of optimally effective therapies. The ALLY-3 and ALLY-3+ phase 3 studies evaluated daclatasvir (DCV) plus sofosbuvir (SOF) with or without ribavirin (RBV) in patients with HCV genotype 3 infection. Here we present safety and efficacy results from an analysis of patients with advanced fibrosis or compensated cirrhosis enrolled in ALLY-3 and ALLY-3+. Methods: HCV genotype 3-infected treatment-naive and -experienced patients received DCV 60 mg + SOF 400 mg without RBV for 12 weeks in ALLY-3 (fibrosis stage F0-F4) or with RBV (weight-based) for 12 or 16 weeks in ALLY-3+ (F3 or F4 only). Due to differences in staging criteria in ALLY-3 and ALLY-3+, categorization of fibrosis stage in ALLY-3 was performed post hoc using ALLY-3+ criteria, and efficacy (sustained virologic response at post-treatment week 12 [SVR12]) and safety outcomes were evaluated in the subset categorized as advanced fibrosis or cirrhosis. Results: Patients with advanced fibrosis or cirrhosis enrolled in ALLY-3 (N = 48) and ALLY-3+ (N = 50) were mostly male (77–80%), white (94–98%) and cirrhotic (69–72%), with high baseline HCV RNA (mean 6.2–6.9 log10 IU/mL). More patients were treatment experienced in ALLY-3+ (74%) than ALLY-3 (38%). In patients with cirrhosis, SVR12 rates were higher in patients receiving DCV+SOF + RBV (86%; 31/36) than in those receiving DCV + SOF (64%; 21/33). Non-response was due to relapse in the majority of cirrhotic patients (ALLY-3: 11/12; ALLY-3+: 4/5). DCV + SOF ± RBV was well tolerated, with no treatment-related deaths, serious AEs, or discontinuations due to AEs; 1 patient died (unrelated to treatment). The most common adverse events (≥10%) were headache and fatigue (both studies), and insomnia, asthenia, and diarrhoea (ALLY-3+). Treatment-emergent Grade 3–4 lab abnormalities were infrequent (Table). Haemoglobin decrease (<9.0g/dL or decrease ≥4.5 g/dL) was observed in one patient receiving DCV + SOF + RBV. Conclusions: Among genotype 3-infected patients with cirrhosis, SVR12 rates were higher among patients receiving DCV + SOF + RBV (86%) than DCV + SOF (64%). DCV + SOF ± RBV was generally safe and well tolerated. DCV + SOF + RBV is a safe and highly efficacious therapy for genotype 3-infected patients with compensated cirrhosis, a population in urgent need of treatment.
BACKGROUND AND AIMS: Patients with co-diagnosis of mental health disease and hepatitis C infection are frequently marginalized with respect to hepatitis treatment. In this study, we address the impact of baseline mental health disease on mental health, SVR12, and adherence to sofosbuvir-based therapy. Methods: Adult patients with chronic hepatitis C genotype 1 infection and treatment naïve were enrolled in 3 clinical studies at the Clinical Research Center of the National Institutes of Health: SPARE (using sofosbuvir and ribavirin), SYNERGY-A, and ERADICATE (both using ledipasvir and sofosbuvir). We identified patients with baseline mental health disease and compared SVR12 and adherence (pill counts, study visits, and blood levels of the sofosbuvir metabolite, GS-331007). For patients with HIV coinfection we also evaluated Becks Depression Inventory scores pre, on, and post treatment and compared these to patients treated with interferon-based therapy. Statistical differences were analyzed by Fisher's Exact, and t-test with significance defined as a p-value less than 0.05. Results: Demographics did not differ between groups. Over 30% of participants were classified as having mental health disease. In all 3 studies a similar percentage of patients with mental health disease achieved SVR12 as without (SPARE: 60.9% compared to 67.6%, p = 0.78; SYNERGY-A: 100% of both groups; ERADICATE: 100% compared to 97.1%). There was no significant difference in pill counts, adherence to study visits, nor in the mean serum concentrations of GS-331007 for each group ( p = 0.72). In patients who had Becks Depression Inventory evaluated, baseline scores were similar but a dichotomous effect was observed with interferon-based (increase on-treatment) and interferon-free (decrease). This difference was statistically significant (p = 0.0011). Post-treatment scores returned to baseline for those on interferon-therapy while patients treated with sofosbuvir-based treatment demonstrated a significant decline in post-treatment BDI-scores compared to baseline (p = 0.001). Conclusions: Direct acting antiviral therapy is well tolerated in patients with mental health disease. These results suggest that these patients can be engaged and treated successfully. Furthermore, our results demonstrate that treatment of chronic hepatitis C with direct acting antiviral therapy may have additional mental health benefits as suggested by a decline in Becks Depression Index.
LEDIPASVIR/SOFOSBUVIR FOR RECURRENT HEPATITIS C IN LIVER TRANSPLANT RECIPIENTS: A REAL-LIFE SPANISH MULTICENTRE EXPERIENCE

Company: Gilead
Drug: Sofosbuvir

Abstract Number: SAT-209

Abstract Body: Background and Aims: Data from phase 2 studies (SOLAR 1 & 2) have demonstrated high SVR12 rates in liver transplant (LT) recipients with HCV recurrence treated with Ledipasvir/Sofosbuvir (LDV/SOF) + Ribavirin (RBV) for 12 or 24 weeks. However, real-life data are lacking in this population. The aim of the present study was to evaluate the Spanish real-life experience with LDV/SOF in a large cohort of patients with recurrent hepatitis C. Methods: Retrospective analysis of data from 381 LT recipients with hepatitis C recurrence who received therapy with LDV/SOF ± RBV in 23 Spanish LT Units from April 1, 2015 to October 31, 2015. Results: Most of the patients were male (69%), IL28B non-CC (75%), with a median age of 62 (31–81) years. 45% of the patients were treatment-experienced and 3% had HIV-HCV co-infection. The genotype distribution was: 1 (n = 342, 90.5%, 1b 72%), 4 (n = 24, 6.3%), and 3 (n = 12, 3%). Fibrosis stage was: F0-F1 (28.5%), F2 (21%), F3 (19%), and F4 (31%). In the patients with cirrhosis, median MELD score was 9 (6–27) and 21% were decompensated (CPT B-C). Treatment duration was 8 (n = 1), 12 (n = 280, 73%) or 24 weeks (n = 100, 26%) with the 24-week regimen being more frequent in patients with cirrhosis than in those with F0-F3 (48% vs 17%, p < 0.0001). RBV was used in 264 (69%) patients with a higher proportion in 12-week schemes (74.6% vs 55%, p = 0.0004). RBV use was not associated with the degree of fibrosis. The median initial RBV dose was 800 mg/d. RBV dose was decreased in 33.5% of the patients and discontinued in 6.4%. Treatment with LDV/SOF was prematurely discontinued in 4 patients, all of them for adverse events (AEs). Currently, 61% of patients have completed antiviral therapy. Rapid virological response was observed in 61% of the patients. In an ITT analysis, SVR4 was 96.5% (109/113) and SVR12 93.4% (54/58). Virological failures (n = 4) were due to premature discontinuations for AEs (n = 2), absence of HCV RNA negativization during treatment (n = 1) and relapse (n = 1). Two patients with cirrhosis died close to the end of therapy for AEs unrelated to therapy (recurrent HCC and sudden death, respectively). Conclusions: The preliminary results of this real-life multicentre cohort suggest that the efficacy of SOF/LDV in recurrent hepatitis C is very high, in line with the results of the phase 2 studies. The use of RBV-free regimens does not seem to impact the efficacy of SOF/LDV in this population and should be further explored in future studies.
Background and Aims: We aimed to investigate the safety and efficacy of interferon (IFN)- and ribavirin (RBV)-free therapy with sofosbuvir plus daclatasvir (SOF/DCV) in HIV/HCV-coinfected patients (HIV/HCV), who have an urgent need for effective antiviral therapy. We also assessed its impact on liver stiffness. Methods: Thirty-four thoroughly documented HIV/HCV with advanced liver disease (advanced fibrosis and/or portal hypertension; n = 31) or severe extrahepatic manifestations (n = 3) who received SOF/DCV were retrospectively studied. The following treatment durations were applied: HCV-genotype (HCV-GT)1/4 without cirrhosis: 12 weeks; HCV-GT1/4 with cirrhosis: 24 weeks; HCV-GT3: 24 weeks; if HCV-RNA was detectable 4 weeks before the end of treatment, treatment was extended by 4 weeks at a time. Results: Fifty percent of patients were treatment-experienced. The majority of patients had HCV-GT1 (67%), while HCV-GT3 and HCVGT4 were observed in 24% and 9% of patients, respectively. Eighty-five percent had liver stiffness >9.5 kPa or METAVIR stage >F2 and 41% had liver stiffness >12.5 kPa or METAVIR stage F4. Portal hypertension (HVPG ≥ 6 mmHg) and clinically significant portal hypertension (HVPG ≥ 10 mmHg) were observed in 64% (18/28) and 25% (7/28) of patients, respectively. The patients with severe extrahepatic manifestations had cryoglobulinemia with leg ulcers or end-stage renal disease, and Non-Hodgkin lymphoma (n = 1 each). Sustained virologic response 12 weeks after the end of treatment (SVR12) was achieved in 100% (34/34) (see Figure panel A). Treatment with SOF/DCV was generally well-tolerated and there were no treatment discontinuations. Among 33 patients with paired liver stiffness measurements, liver stiffness decreased in 88% (29/33) of patients, while it increased in 12% (3/33) of patients (see Figure panel B). There was a decrease in liver stiffness between BL and FU (11.4 [10] vs. 6.9 [7.35] kPa; mean change: −4.41 ± 0.79 kPa; p < 0.001; see Figure panel B). The mean relative change in liver stiffness was −27 ± 4%. Conclusions: IFN- and RBV-free treatment with SOF/DCV was well-tolerated and achieved SVR12 in all difficult-to-treat HIV/HCV. It also significantly improved liver stiffness, suggesting anti-fibrotic and anti-portal hypertensive effects.
EFFECTIVENESS OF LEDIPASVIR/SOFOSBUVIR AND OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR IN TREATMENT-NAÏVE AND –EXPERIENCED U.S. VETERANS WITH GENOTYPE 1 HEPATITIS C INFECTION

Company          Gilead
Drug             Sofosbuvir

Abstract Number  SAT-216

Abstract Body: Background and Aims: Sustained virological response rates (SVR) after interferon-based antiviral therapies have been traditionally lower in U.S. Veterans compared to Non-Veterans. Limited data are available for new all oral HCV therapy. We therefore assessed the effectiveness of ledipasvir/sofosbuvir ± ribavirin (LDV/SOF ±RBV) given for 8–24 weeks or ombitasvir/paritaprevir/ritonavir/dasabuvir ± ribavirin (OMB/PAR/RIT/DAS ± RBV) given for 12 weeks in treatment-naïve and –experienced genotype 1 (GT1) hepatitis C virus (HCV)-infected U.S. Veterans treated at a single VA transplant center. Methods: From January until September 2015, 335 Veterans with GT1 infection (1:32;1a:220;1b:83) were started on all oral antiviral therapy; for the entire cohort, SVR12 data will be available by March 2016. 62% of Veterans had cirrhosis and 30% were treatmentexperienced. RBV was added to LDV/SOF for those who were treatment-experienced (n = 78) to shorten treatment duration to 12 weeks and was tolerated well. LDV/SOF was given for 8 and 24 weeks in 30 and 16 Veterans, respectively. All other Veterans were treated for 12 weeks. SVR 12 data were determined from HCV-RNA levels available through November 21, 2015 and obtained 12 weeks or later after end of antiviral therapy. Results: Of these 132 veterans the overall SVR 12 rate was 92% (121/132). 2 Veterans with Child Pugh B cirrhosis expired during therapy due to events unrelated to drug therapy. Viral breakthrough and relapse occurred in 3 Veterans, respectively. Drug-related adverse events resulted in early termination of therapy in an additional 3. Of those treated with OMB/PAR/RIT/DAS ± RBV, the SVR rate was 89% (16/18) compared to LDV/SOF ± RBV with a SVR rate of 96% (105/109). Among all cirrhotic Veterans started on therapy, SVR 12 rates were 82% (86/95) compared to 90% and 75% for those on LDV/SOF ± RBV and OMB/PAR/RIT/DAS ± RBV regimens, respectively. Conclusions: In this large cohort of treatment-naïve and -experienced GT1 HCV-infected Veterans, high SVR12 rates were obtained with either LDV/SOF ± RBV or OMB/PAR/RIT/DAS ± RBV, respectively. Although less Veterans had been treated with OMB/PAR/RIT/DAS ± RBV, SVR rates may be higher, particularly in the presence of cirrhosis, when LDV/SOF ± RBV is used. Adding RBV to LDV/SOF does not compromise SVR rates and was cost-effective. SVR12 data for the entire cohort of 335 U.S. Veterans will be presented.
Background and Aims: Hepatitis C virus (HCV) recurrence is universal among liver transplant (LT) recipients. It is associated with recurrence of cirrhosis, graft failure and re-transplantation. Newer generation direct-acting anti-viral (DAA) agents; ledipasvir (LDV)/Sofosbuvir (SOF) have excellent rates of sustained virologic response (SVR). However, only limited data is available regarding the efficacy and safety of these agents in LT recipients. To evaluate the efficacy and safety of LDV/SOF therapy in LT recipients with HCV recurrence. Methods: Retrospective review of 96 LT recipients with HCV recurrence who received LDV/SOF therapy between December 2014 and October 2015. 54 LT recipients with SVR12 data were included in analysis; 42 did not have SVR12 information and were excluded. Baseline clinical/demographic characteristics, SVR12, graft function, changes in immunosuppression, adverse events and survival rates were collected. Results: 54 LT recipients with SVR12 information were included. 76% were male and 59% Caucasians. Mean age was 62 ± 6 years. Genotype distribution: 93% was genotype 1 and 3.5% each were genotype 3 and 4. 17% had cirrhosis and 8% had high grade fibrosis. 41% were treatment naïve and 59% were treatment-experienced. 11% had failed prior sofosbuvir (SOF) based therapy. 70% received “dual” therapy with ribavirin. Overall SVR12 was 98%; 89% among cirrhotic patients. Only 1 patient with genotype 3 who had failed prior SOF based therapy, failed LDV/SOF therapy. 54% reported minor adverse events; however, no serious adverse events were reported. 6% were hospitalized during HCV treatment for biliary stricture, near syncope and anemia. No death, liver graft rejection/failure, discontinuation of treatment or changes in immunosuppression was recorded. Conclusions: LDV/SOF therapy is effective and safe amongst LT recipients with HCV recurrence including those with graft cirrhosis.
LEDIPASVIR/SOFOSBUVIR FOR 8 WEEKS IN NON-CIRRHOTIC, TREATMENT NAIVE PATIENTS WITH GENOTYPE 1 HEPATITIS C INFECTION: REAL LIFE EXPERIENCE IN A COMMUNITY SETTING

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-227

Background and Aims: Hepatitis C treatment has evolved a long way from 78 weeks interferon monotherapy to 48 weeks pegylated interferon plus ribavirin therapy to the most recent 12 weeks therapy with newer direct-acting antiviral (DAA) agents such as ledipasvir or sofosbuvir (LDV/SOF). Ever since the emergence of newer generation DAAs, HCV treatment has been revolutionized with their excellent sustained virologic response (SVR), tolerable side effect profiles and shorter duration of therapy. ION-3 trial has demonstrated that 8 weeks therapy, with LDV/SOF in non-cirrhotic, treatment naïve patients with genotype 1 infection, is non-inferior to 12 weeks therapy without significant change in SVR. Adding ribavirin to 8 weeks therapy with LDV/SOF did not show any additional benefit. The shorter duration of treatment can remarkably increase patient compliance and decrease the cost. We aim to evaluate the efficacy of 8 weeks LDV/SOF therapy among non-cirrhotic, treatment naïve patients with genotype 1 infection.

Methods: Retrospective review of 242 non-cirrhotic patients with genotype 1 infection who received LDV/SOF therapy for 8 weeks from December 2014 to July 2015. 2 patients who discontinued treatment were excluded. All patients had 6 million or less viral load prior to treatment. Patients’ baseline clinical and demographic characteristics, SVR rates and adverse events were collected.

Results: Of 240 patients in this cohort, 58% were male and 53% were Caucasians. Mean age was 57 ± 10. While 96% patients had never received HCV treatment, 4% were treatment-experienced: 9 had failed prior pegylated-interferon and ribavirin, 1 had failed prior pegylated-interferon, ribavirin and boceprevir therapy. Overall SVR 12 was 98%. 99% of treatment naïve patients and 80% of treatmentexperienced patients achieved SVR 12. 2 patients had to discontinue the drug due to severe rash and profound edema. >50% patients reported minor adverse events, however, no serious adverse events, liver decompensation or death were reported.

Conclusions: Excellent efficacy with a high rate of SVR was seen amongst non-cirrhotic, treatment naïve patients with genotype 1 infection who were treated with LDV/SOF therapy for 8 weeks. The outcomes of our study are comparable to as of ION-3 clinical trial.
Background and Aims: Sofosbuvir/Ledipasvir (SOF/LDV) is highly effective in treating patients with genotype (GT) 1, 4, 5 and 6 hepatitis C. Real world cohort data from the United States have highlighted a reluctance to use 8 week treatment regimens in eligible non cirrhotic patients, and suggested that proton pump inhibitor (PPI) use may have a detrimental impact on sustained viral response (SVR) rates. We sought to examine the impact of these, and other baseline factors in patients attending our treatment centres. Methods: The Scottish Hepatitis C database was examined to identify patients commencing treatment with SOF/LDV in Glasgow treatment centres prior to 01/10/2015. Patients were treated to a local protocol; Treatment naive F0-3 patients (liver stiffness <12.5kPa/11.9 kPa (HIV co-infected)) were treated for 8 weeks, irrespective of baseline viral load and HIV status. All other patients were treated for 12 weeks with addition of Ribavirin (RBV) post liver transplant, in decompensated cirrhosis, treatment experienced cirrhosis, platelets <75 and protease inhibitor (PI) failures. All patients underwent a screen for drug-drug interactions (DDIs) and PPI dose was reduced to omeprazole 20 mg (or equivalent) with appropriate dosing instructions. Standard practice was to dispense SOF/LDV from a community pharmacy, with directly observed therapy where appropriate. Data on demographics, liver disease severity, methadone use, treatment regimens, on treatment response, SVR and premature discontinuation were obtained from the database augmented by chart review. Viral RNA was tested using Abbott Realtime PCR, lower limit of quantification (LLOQ) 12 IU/mL. Results: Demographics and baseline characteristics are displayed in Table 1. The cohort are predominantly male, over 80% have advanced fibrosis (1:10 Child’s B/C), around 1 in 3 are treatment experienced, and high levels of opiate substitution, PPI use and drug of abuse use were seen. To date 108 patients have completed treatment. 1 patient discontinued treatment early due to non compliance; no discontinuations due to adverse events have been seen. 41/45 (91%) of patients have achieved SVR12 (8/8 (100%) treated for 8 weeks), 33/37 (89.1%) of those treated for 12 weeks). Full SVR12 data analysed according to baseline factors will be presented. Conclusions: Sofosbuvir/Ledipasvir is well tolerated in a difficult to treat real world cohort, with SVR12 rates comparable to clinical trials.
DETERMINATION OF LEDIPASVIR CONCENTRATIONS IN PATIENTS WITH DECOMPENSATED CIRRHOSIS RECEIVING LOW DOSE PROTON PUMP INHIBITORS DURING SOFOSBUVIR-LEDIPASVIR TREATMENT FOR HCV GENOTYPE 1 INFECTION

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-233

Background and Aims: The combination of sofosbuvir-ledipasvir is associated with high sustained virologic response (SVR) rates in HCV genotype 1 infection, even in patients with decompensated cirrhosis. However, drug-drug interactions remain an important consideration in patients undergoing therapy. Recent real world data has suggested that pre-treatment proton pump inhibitor (PPI) therapy may be associated with a reduced efficacy of therapy containing ledipasvir. The current recommendation is that PPI dosage should be reduced prior to treatment with sofosbuvir-ledipasvir. Methods: Plasma trough concentrations were prospectively collected in 32 decompensated cirrhotic patients receiving 12 weeks of sofosbuvir-ledipasvir therapy for HCV genotype 1 infection. GS-331007 (major circulating metabolite of sofosbuvir) and ledipasvir plasma trough samples were collected at treatment days 7, 14, 28, and 84 and measured using validated LC-MS/MS. 15 patients were receiving PPI therapy at baseline, and had dosage reduction to the equivalent of 20 mg omeprazole or 15 mg lansoprazole, and were advised not to take their PPI prior to the sofosbuvir-ledipasvir dose. Plasma trough levels of ledipasvir were compared in those on PPI therapy vs no PPI therapy. Results: Mean age was 52.81 ± 10.4 and 62.5% were male. The median MELD score was 10 ± 3.2. All patients achieved an on-treatment virologic response, and the SVR12 rate was 87%. There was no significant difference in mean trough ledipasvir concentrations in patients receiving low dose PPI therapy vs no PPI (145.9 ng/mL vs 175.4 ng/mL – p = 0.272). Conclusions: In our patient cohort, there was no reduction in ledipasvir trough concentrations in patients receiving low dose PPI therapy. These preliminary data do not exclude a significant effect of PPI on ledipasvir concentrations, and larger pharmacokinetic-pharmacodynamic studies are required. Patients receiving PPI therapy should have their dose reduced prior to therapy.
Background and Aims: Ledipasvir/Sofosbuvir (LDV/SOF) for 8–24 weeks is approved for the treatment of chronic hepatitis C. In the ION-3 study 8 weeks of LDV/SOF was non-inferior to 12 wks in previously untreated GT1 patients without cirrhosis. According to the summary of product characteristics (SmPC) a treatment duration of 8 wks may be considered in naïve non-cirrhotic HCV GT1 infected patients with viral load <6 Mio IU/mL. Aim of this analysis was to evaluate the virologic response rates of 8 wks treatment under real world conditions.

Methods: The DHC-R (Deutsches Hepatitis C-Register) is a registry for the documentation of the HCV treatment situation in Germany. Data are collected in a centralized database and on-site monitoring is implemented. Data collection is ongoing. In this analysis data of patients with 8 or 12 wks treatment with LDV/SOF and available SVR12 data (until 9/2015) were included. Baseline characteristics, prior treatment history, safety and effectiveness were investigated.

Results: 262 (141 female) pts (8 week) and 444 (210 female) pts (12 week) met the inclusion criteria. One pt in the 8 week group (1) and 130 in the 12 week group (2) had weight-based ribavirin added to LDV/SOF. The mean (SD) age was 50.4 (13.1) yrs in group 1, 55.0 (12.6) in group 2. Genotype distribution was 98.1% for GT1 and 1.9% GT4. In 37% the fibrosis stage was evaluated by elastography (Fibroscan), the mean (SD) stiffness value in group 1 was 6.2 kPa (2.4) and 10.4 kPa (8.1) in group 2. One pt in group 1 had a liver stiffness ≥16.5 kPa, 8 were categorized as cirrhotic (2 relapses). Mean HCV RNA at baseline was 1,606,548 IU/mL (3,375,284) in group 1 and 2,727,867 IU/mL (6,227,207) in group 2. Seven pts of group 1 had a baseline viral load >6 Mio IU/mL (1 relapse). 17 pts in group 1 were HIV co-infected, 24 pts received substitution treatment. 24 pts in group 1 had prior treatment. SVR12 (ITT) in group 1 was 88.5% (232/262) (13 relapses documented, SVR12 not determined in 17) and 92.6% (2.5% not determined) in group 2. Three out of the yet documented 20 relapses occurred in pts treated outside the selection criteria. In the per protocol analysis the SVR12 rates were 95.5% and 95.1% in group 1 and 2, respectively. Conclusions: Under real world conditions, 8 wks LDV/SOF achieves comparable SVR rates to 12 weeks treatment, but relapses are more frequent in particular in patients who do not meet the selection criteria according to the SmPC.
LEDIPASVIR/SOFOSBUVIR (LDV/SOF) FOR 8 WKS IN GENOTYPE 1 (GT1) TREATMENT-NAÏVE NON-CIRRHOTIC PATIENTS WITH HCV VIRAL LOAD <6 MILLION IU/ML (6M); A COMPARATIVE ANALYSIS OF THE PHASE-3 ION-3 DATA TO REAL WORLD EFFECTIVENESS

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-242

Abstract Body

Background and Aims: The optimal duration of therapy to achieve SVR depends on multiple factors. Patients treated with LDV/SOF with 8–24 weeks achieved SVR12 from 94% to 100% in the ION Phase 3 studies. A decision to shorten therapy to 8 weeks is based on treatment history, cirrhosis status and baseline viral load (VL). In a post-hoc analysis of the ION-3 (treatment naive (TN), non-cirrhotic (NC patients)) 8 week data, a VL < 6 M was shown to be the best predictor of SVR. Real world effectiveness (RWE) is often different from Phase III trials and there is a need to understand real-world 8 week regimens in a broader spectrum of patients.

Methods: RWE 8 week LDV/SOF data is emerging from multiple single-center and multicenter retrospective and prospective cohorts. In this analysis, the phase-3 ION-3 data is compared with data from several diverse real world populations and one post-marketing investigator sponsored HIV/HCV trial. Patient demographics, characteristics, SVR12 and discontinuation data has been collated and compared. Results: The ION-3 post-hoc analysis reported 123 patients who were TN, NC and VL < 6 M and treated with 8 weeks of LDV/SOF. Mean age was 52, 22% black, 72% GT1a; the SVR12 was 97% (119/123). The overall SVR12 rate from six diverse real world and post marketing cohorts was also 97% (638/658). There was no significant impact of HCV genotypes or subtypes (GT1a, 1b versus GT4), prior treatment history, presence or absence of cirrhosis, high viral load (HCV VL > 6 M), or HIV/HCV co-infection. All response rates are detailed in Table 1. Conclusions: LDV/SOF for 8 weeks yielded high SVR rates in ION-3. Analysis of RWE data from several diverse & heterogeneous cohorts from the US & EU show SVR outcomes that were consistent with the Phase-3 ION-3 results and supports the use of 8 weeks LDV/SOF in treatment-naive, non-cirrhotic GT1 patients with a baseline HCV VL < 6 M and possibly in other populations including HIV/HCV coinfected patients. Discontinuation rates were low despite diverse patients and clinical settings. Data from the TARGET and TRIO cohorts also suggests that the 8-week regimen is underutilized.
EXCELLENT EFFICACY AND TOLERANCE OF INTERFERON FREE REGIMEN BASED SOFOSBUVIR AND THEIR IMPACT IN ALCOHOL WITHDRAWAL IN HEAVY DRINKERS INFECTED WITH HCV

**Company**
Gilead

**Drug**
Sofosbuvir

**Abstract Number**
SAT-250

**Abstract Body**

Background and Aims: The treatment of HCV with pegylated interferon and ribavirin in alcoholic patients was associated with more early withdrawals,1 particularly because of psychiatric side effects. The purpose of the study was to assess the impact of chronic alcohol intoxication on compliance and efficacy of treatment with directs anti viral agents (DAAs). Methods: Twenty-eight patients (24 M, 4 F) infected with HCV, mean age 52.1 ± 5.7 years were included. Among them, 26 patients were alcohol-dependent and 2 had an abuse according to DSM IV classification. All had a CAGE score ≥2 at baseline. DAAs therapy was initiated in the immediate alcohol withdrawal. The following regimens used were: sofosbuvir + ribavirin (3), sofosbuvir + Daclatasvir ± ribavirin (9), sofosbuvir + Simeprevir (5) and sofosbuvir + ledipasvir ± ribavirin (11). The duration of treatment was 12 or 24 weeks. A close nurse, psychiatric, hepatic monitoring and a regular monitoring of the addiction were implemented during treatment and follow-up phase. Results: At baseline, the average daily amount of alcohol consumed was 126 ± 74.4 grams per day. The average duration of alcohol consumption was 25.2 ± 6.7 years. Fifteen patients (54%) were naive of HCV treatment. The patients had a genotype 1a (46.4%), 1b (7.1%), 3 (21.4%) or 4 (25%). Twenty-two patients (79%) had cirrhosis (F4) and 6 patients (21%) had F3 fibrosis score. To date, 24 patients have completed treatment and achieved the week 4 follow up. Twenty-one patients were followed-up at week 12. There were no early DAAs withdrawal or lost of follow up. There were no unexpected adverse side effects. Twenty-four patients (100%) achieved virological response at the end of treatment and had SVR 4 and 21 patients (100%) had SVR 12. At SVR 12, 11 patients (52.4%) were always weaned of alcohol. Among the 10 patients (47.6%) not weaned, daily alcohol consumption remained lower than that seen at baseline (61.0 ± 43.6 vs 130.0 ± 59.6 grams per day, p = 0.008). Conclusions: Tolerance and observance of interferon free regimen based on sofosbuvir are excellent in alcoholic heavy drinkers. SVR is identical to that seen in non-alcoholic population, even in the event of continued alcohol consumption. This pilot study shows that the access of DAAs for alcohol-dependent patients with HCV should be facilitated and that the cure of HCV could help these patients for alcohol withdrawal.
Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-280

Abstract Body: Background and Aims: Identification of subgroup differences in response to treatment with direct acting antiviral agents could help determine the optimal treatment strategy for individual patients and populations. "Intention-to-treat" analyses that conflate drug efficacy with patient adherence may obscure important biological differences in rates of sustained virological response (SVR). Previously, we demonstrated that gender and IFNL4 rs12979860 ("IL28B") genotype were associated with SVR in "per-protocol" analyses of treatment with ledipasvir/sofosbuvir for 8 weeks (ION-3). We now extend that effort to include data from additional trials of ledipasvir/sofosbuvir. Methods: We calculated SVR based on viral relapse after treatment with ledipasvir/sofosbuvir using data from publications that included a patient group in which at least 10 patients suffered relapse. Three groups of HCV genotype 1 infected patients were included: ION-3 (n = 423, non-cirrhotic treatment-naïve patients, 8 weeks treatment); ION-4 (n = 322, HCV/HIV co-infected patients, 12 weeks treatment); pooled publication of compensated cirrhosis (n = 307, patients from 7 clinical trials, 12 weeks treatment). We combined data on gender and rs12979860 (three genotype categories) using Cochran-Mantel-Haenszel statistics. Results: Among cirrhotic patients and ION-3 participants, SVR rates were ~99% for women and ~93% in men (Table 1). In ION-4 the SVR rate in women was ~97% among female subjects (n = 56) and also in men. Overall, women had significantly higher SVR rates than men (p = 0.0007) and were ~4 times less likely to suffer viral relapse. For rs12979860, SVR rates were 98–100% in individuals with rs12979860-CC genotype and 90–91% in those with the rs12979860-TT genotype (Table 1; data on rs12979860-TT were unavailable for the cirrhotic patients). Combining ION-3 and ION-4 data revealed a highly significant association (p = 0.0002) among the three genotype categories; patients with rs12979860-TT genotype were ~4.5 times more likely to relapse than those with rs12979860-CC. Individual level data needed for analyses combining gender and rs12979860 were unavailable. Conclusions: Gender and IFNL4 rs12979860 genotype are strong predictors of response to ledipasvir/sofosbuvir. These subgroup differences could facilitate more efficient and cost effective treatment of chronic hepatitis C.
Background and Aims: HCV-infected patients with decompensated cirrhosis are one of the most difficult-to-treat populations. At present, limited data are available to support decisions regarding transplantation versus continued antiviral therapy. This analysis reports interim results from a large multicentre compassionate use programme (ATU) in France. Methods: More than 4,000 patients with severe fibrosis or cirrhosis have received once-daily daclatasvir (DCV 60 mg) + sofosbuvir (SOF 400 mg) in the French ATU since 2014. The recommended duration of therapy (DoT) was 24 weeks; physicians could add ribavirin (RBV) or reduce DoT at their discretion. The present analysis is based on patients with decompensated cirrhosis (Child-Pugh B or C). The objectives of this interim analysis were to evaluate sustained virological response at posttreatment week 12 (SVR12) and liver function outcome based on changes in Child-Pugh score at posttreatment week 12 or end of treatment. Results: A total of 257 patients with decompensated cirrhosis had been included in the cohort; this interim analysis was restricted to 93 patients. At baseline, patients were 77% male with a median age of 55 years; 70 (75%) were treatment-experienced (including 26 prior protease inhibitor failures); 19 (20%) were HIV coinfected. Child-Pugh was B in 85 patients (91%) and C in 8 patients (9%). Median platelet count was 74 × 10⁹/L; median albumin, 30 g/L; median total bilirubin, 34 μmol/L; median MELD score, 13. Ascites and encephalopathy were present in 32 (34%) and 7 patients (8%), respectively. Most patients received DCV + SOF without RBV (80%) and were treated for 24 weeks (84%). SVR12 was achieved in 70/85 patients (82%) and C in 8 patients (9%). Median platelet count was 74 × 10⁹/L; median albumin, 30 g/L; median total bilirubin, 34 μmol/L; median MELD score, 13. Ascites and encephalopathy were present in 32 (34%) and 7 patients (8%), respectively. Most patients received DCV + SOF without RBV (80%) and were treated for 24 weeks (84%). SVR12 was achieved in 70/85 (82%) Child-Pugh B patients and 8/8 Child-Pugh C patients (100%). Seven patients experienced relapse, 3 had viral breakthrough, 3 had detectable HCV RNA at end of treatment and 2 had undefined virological failure. A Child-Pugh score was available at posttreatment Week 12 or end of treatment in 52 patients; the majority returned to Child-Pugh A (Table). In parallel, the median MELD score dropped to 11. There were 2 discontinuations due to adverse events, 1 due to onset of a contraindication, 1 for unknown reasons, and 2 deaths. Conclusions: In this real-life cohort, 78 of 93 patients (84%) with decompensated cirrhosis achieved SVR12. The majority of patients with virological response experienced clinical improvement. Updated data in a larger population are planned for the final presentation.
Background and Aims: HCV treatment regimens with direct-acting antivirals have not been extensively studied in patients with decompensated cirrhosis. The aim of this study is to assess patient-reported outcomes (PROs) in patients with decompensated cirrhosis who were treated with a fixed-dose combination of sofosbuvir/velpatasvir (SOF/VEL) with and without ribavirin (RBV).

Methods: Four PRO questionnaires (SF-36, CLDQ-HCV, FACIT-F, WPAI: HCV) were administered prospectively in a phase 3 clinical trial of SOF/VEL in decompensated patients with HCV (ASTRAL-4). Results: A total of 267 patients with decompensated cirrhosis were enrolled (57.8 ± 6.4 years, 70% male, 78% HCV genotype 1, 15% HCV genotype 3, 45% treatment-naïve, 80% with baseline ascites, 62% baseline encephalopathy, 6% with Child-Pugh score of 5–6, 90% with 7–9, 4% with 10–12). The SVR-12 rates were 84.4% in SOF/VEL and 94.3% in SOF/VEL + RBV (p = 0.02). Baseline clinico-demographic characteristics and PRO scores were similar (all p > 0.05). In both SOF/VEL and SOF/VEL + RBV groups, statistically significant improvements in some of the PROs, including general health, emotional well-being and worry scores (up to +11.9 points on a universal 0–100 PRO scale in SOF/VEL + RBV, up to +16.6 in SOF/VEL, p < 0.05), were observed shortly after the start of treatment (4 to 8 weeks), and continued throughout the duration of treatment. At week 12 and 24 follow-ups, no differences in PROs were noted between the treatment arms (all p > 0.05), and improvements in most of the PROs were observed in SOF/VEL both with and without RBV (up to +19.3 points, average across all studied PRO domains +8.5 points). In multivariate analysis, the major baseline predictors of PRO impairment were the presence of ascites, encephalopathy, pretreatment history of insomnia and depression. Conclusions: Patients with HCV-related decompensated cirrhosis treated with SOF/VEL+RBV achieved 94.3% SVR-12. Furthermore, there is significant early and sustained improvement of PROs posttreatment with SOF/VEL with or without RBV in patients with HCV-related decompensated cirrhosis.
EFFECTIVENESS AND SAFETY OF SOFOSBUVIR/LEDIPASVIR TREATMENT FOR MONOINFECTED GENOTYPE 1 HCV PATIENTS IN REAL-LIFE CLINICAL PRACTICE: RESULTS FROM SPANISH HEPA-C COHORT

**Company**  
Gilead

**Drug**  
Sofosbuvir

**Abstract Number**  
LBP511

**Abstract Body**  
Introduction: The Sofosbuvir/Ledipasvir (SOF/LDV) combination has shown high rates of cure and a good safety profile in clinical trials. The main end-point analyzed effectiveness and safety of SOF/LDV combination (with or without ribavirin) in patients with HCV genotype 1 infection. Material and Methods: The study included 1,957 patients from the Spanish Cohort, a multicenter, collaborative (40 hospitals), and observational cohort. HCV genotype 1 infected patients who started SOF/LDV treatment before October 31th, 2015, were included. The exclusion criteria were co-infection with HBV or HIV, hepatocellular carcinoma, and liver transplant recipients. Patients with at least a SVR4 post-treatment were included for analysis. Results: From the whole cohort, 1,778 had SVR4 data. Most of the patients were male, mean age 58.6 years old, and the mean viral load of 6.62 log. Genotype distribution: 1a- 29.8%, 1b- 65.9%, 1-non specified 4.1%. Most of the patients were cirrhotic (F0-1: 8.3%, F2: 18.1%, F3: 19.8% and F4: 53.9%). Ribavirin was added per physician discretion in 29.7% of the regimens. Treatment duration: 8-weeks (4.1%), 12-weeks (73.5%) and 24-weeks (21.4%). 61.2% were treatment experienced, including first generation protease inhibitors (PI) failures (9.8%). SVR4 was 96.3%, which was independent of gender, genotype subtype, fibrosis stage, ribavirin use and previous treatment response, including PI failures. 95.7% of cirrhotic patients achieved SVR4. 3.7% of the patients experienced treatment failure; 1.6% due an early discontinuation caused by an adverse event, 1.9% of the patients went through virological failure and 0.3% voluntary withdrawal. Although fibrosis was not a negative predictive factor of response, bilirubin >2 mg/dL and albumin <3.5 g/dL were SVR predictors. Safety: 5.3% of the patients developed severe adverse events; 3.7% had an early discontinuation, 1.6% owing to adverse events. Twelve patients died, in most of the cases there was no relationship with the antiviral treatment. Conclusion: This study demonstrates the high effectiveness and safety of the SOF/LDV regimen for HCV treatment in real-life clinical practice. Rates of cure were independent of fibrosis stage, and previous response. Although there were many patients with advanced liver disease, severe adverse events and early discontinuations were very low. Hyperbilirubinemia (>2 mg/dL) and hypoalbuminemia (>3.5 g/dL) were found to be significant negative predictors of response.
### SIMEPREVIR PLUS SOFOSBUVIR FOR HEPATITIS C VIRUS GENOTYPE 4 INFECTION: A PHASE 3, OPEN-LABEL STUDY

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>LBP516</td>
</tr>
</tbody>
</table>

#### Abstract Body

**Introduction:** The Phase 3, open-label, single-arm PLUTO study (HPC3021; NCT02250807) is investigating the efficacy and safety of 12 weeks of simeprevir (NS3/4A protease inhibitor) + sofosbuvir (NS5B polymerase inhibitor) in treatment-naïve or (Peg)interferon [IFN] ± ribavirin [RBV])-experienced hepatitis C virus (HCV) genotype (GT)4-infected patients. Material and Methods: Patients received simeprevir 150 mg once daily (QD) + sofosbuvir 400 mg QD for 12 weeks. The primary efficacy endpoint was sustained virologic response 12 weeks after the actual end of treatment (SVR12). Superiority would be confirmed if the lower limit of the SVR12 95% Clopper-Pearson confidence interval (CI) was greater than a historical control rate (a composite of the SVR12 rates from the Phase 3 RESTORE study in HCV GT4-infected patients treated with simeprevir + PegIFN/RBV for each of the subpopulations enrolled). Results are presented from the primary analysis, when all patients reached the SVR12 time point. Results: 40 patients received treatment (male, 29/40 [73%]; mean age, 51 years; IL28B non-CC, 34/40 [85%]; GT4a/4d/4f, 10/40 [25%]/29/40 [73%]/1/40 [3%]; compensated cirrhotic, 7/40 [18%]; median baseline HCV RNA, 6.35 log10 IU/mL [range: 4.8–7.2]; treatment-naïve, 13/40 [33%]; treatment-experienced, 27/40 [68%]; prior relapser, 2/40 (5%); prior non-responder, 21/40 (53%); IFNintolerant, 1/40 (3%)]. All 40 patients achieved SVR12 (100% [95% CI: 91, 100]), demonstrating superiority versus the historical control (61%). Adverse events (AEs), all Grade 1 or 2, were observed in 20 (50%) patients. No serious AEs were reported and no patients discontinued study treatment due to AEs. The most frequent AEs (in ≥2 [5%] patients) were headache (20%), asthenia (8%), catarrh (8%), constipation (5%), erythema (5%), and rash (5%). Grade 3 treatment-emergent laboratory abnormalities were confirmed in 2 (5%) patients, each with transient and asymptomatic elevation of pancreatic enzymes. Conclusion: The PLUTO study showed a 100% SVR12 rate with 12 weeks of treatment with simeprevir + sofosbuvir in patients infected with HCV GT4, irrespective of stage of fibrosis or prior treatment with (Peg)IFN ± RBV. The regimen was generally safe and well tolerated.
# HCV ERADICATION RESULTS IN REDUCTION OF HEPATIC VENOUS PRESSURE GRADIENT 48 WEEKS AFTER END OF TREATMENT; FINAL RESULTS OF THE STUDY OF SOFOSBUVIR PLUS RIBAVIRIN IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION

**Company**  
Gilead

**Drug**  
Sofosbuvir

**Abstract Number**  
LBP518

**Abstract Body**

Introduction: Portal hypertension is a predictor of liver-related clinical events, mortality and response to antiviral treatment in patients with HCV infection and cirrhosis. The effect of interferon-free HCV treatment on portal pressure is unknown. Material and Methods: Fifty Child-Pugh-Turcotte (CPT) A and B cirrhotic patients with portal hypertension (hepatic venous pressure gradient [HVPG] >6 mmHg) were randomized to receive 48 weeks of open-label SOF + RBV at Day 1 or after a 24-week observation period. The primary endpoint was SVR12. Secondary endpoints included changes in HVPG at end of treatment, laboratory parameter values, MELD, and CPT scores. We report the results of follow-up through post-treatment Week 48 in a subset of patients subsequent to a protocol amendment. Results: Overall, SVR12 was achieved in 72% (33/46; 4 patients in the observation arm discontinued prior to starting study drug). Of the 33 subjects with pre-treatment clinically significant portal hypertension (HVPG ≥ 12 mm Hg) and paired HVPG results for baseline and end of treatment (EOT), 76% (25/33) achieved SVR12 and there was a mean change in HVPG of −1.1 mm Hg (p = 0.1331 with 1-sample t-test). Nine patients who completed treatment with an SVR12 agreed to an HVPG measurement at Week 120 (post-treatment Week 48). These patients were predominantly male (78%), Caucasian (100%), prior treatment failures (89%), genotype 1 (56%) with mean baseline HCV RNA 6.1 log10 IU/mL, CPT score 6 and MELD score 10. Overall there was a 29% reduction in mean HVPG from baseline to post-treatment Week 48 (p = <0.0001 with 1-sample t-test; see Figure). Eight had a ≥20% reduction in HVPG and three reduced their pressure to <12 mm Hg. Conclusion: SOF + RBV for 48 weeks resulted in an SVR rate of 72% and was associated with reductions in HVPG. Clinically meaningful HVPG reductions (≥20%) were observed in only 24% (8/33) of patients at end of treatment but in 89% (8/9) at post-treatment Week 48. These results suggest that continued improvement in liver physiology, as measured by HVPG, is possible post SVR and may result in better long-term clinical outcomes after DAA therapy.
NO EFFECT OF PROTON PUMP INHIBITOR (PPI) USE ON SVR WITH LEDIPASVIR/SOFOSBUVIR (LDV/SOF): REAL WORLD DATA FROM 2034 GENOTYPE 1 PATIENTS IN THE TRIO NETWORK

Company
Gilead

Drug
Sofosbuvir

Abstract Number
LBP519

Abstract Body
Introduction: PPI use may reduce the AUC for ledipasvir and could impact SVR in patients treated with LDV/SOF. An incomplete report from the HCV TARGET network suggested that PPI use at baseline was associated with a 5% reduction in SVR12 (Terrault, AASLD 2015); however data regarding the actual PPI, duration of use and dosage was not available. The aim of this study is to evaluate type of PPI, dose and duration of PPI treatment on SVR in real-world patients treated with LDV/SOF.

Material and Methods: Data were collected from providers and specialty pharmacies through Trio Health’s Innervation Platform, a cloud-based disease management program which allows comprehensive evaluation of concomitant medication, including PPI type, dose and duration. All genotype 1 HCV patients who initiated treatment with 8, 12, or 24 weeks of LDV/SOF ± RBV between Oct 2014 and Mar 2015 were included in the analysis (n = 2,034). Results: Demographics of the 2,034 patients showed that 68% were genotype 1a, 35% cirrhosis, 94 patients received RBV and 42% prior treatment failure. 468 patients (23%) were on a daily PPI (omeprazole 63%, esomeprazole 11%, pantoprazole 17%) with 120 patients (26%) taking high dose twice daily PPIs during their course of LDV/SOF treatment. Overall SVR12 by ITT was 95% (1,938/2,034); of the 96 patients who did not achieve SVR, 22 discontinued treatment, 33 were lost to follow up, and 41 completed therapy and were relapers. Per protocol analysis (n = 1,979), overall SVR12 rate was 98% (1,938/1,979). SVR was 97% (441/454) for those on a PPI during treatment, and 98% (1,497/1,525) for those not on a PPI. All patients on H2 blockers achieved SVR. Multivariate analysis showed only fibrosis score (p = 0.0013) and duration of HCV treatment (0.0360) to be predictors of SVR. A matched propensity analysis for patients on PPI compared with no PPI use showed no effect of PPI on SVR. Conclusion: Daily PPI did not have an effect on SVR in a heterogeneous real-world US population and suggests that LDV/SOF can be safely used in HCV genotype 1 patients according to current prescribing information.
EVIDENCE OF IMPRESSIVE REAL WORLD SVR FROM THE PORTUGUESE LEDIPASVIR/SOFOSBUVIR AND SOFOSBUVIR UNIVERSAL COVERAGE PROGRAM TO ERADICATE (ELIMINATE) HEPATITIS C

Company: Gilead
Drug: Sofosbuvir

Abstract Number: LBP523

Abstract Body:

LBP523 EVIDENCE OF IMPRESSIVE REAL WORLD SVR FROM THE PORTUGUESE LEDIPASVIR/SOFOSBUVIR AND SOFOSBUVIR UNIVERSAL COVERAGE PROGRAM TO ERADICATE (ELIMINATE) HEPATITIS C

J. Rodrigues1, R. Tato-Marinho2, H. Mota-Filipe1,3, A.P. Martins3, J.C. Martins1, V. Andreozzi4, B. Vandewalle4, J. Félix4, E.C. Alves1. 1 Infarmed – National Authority of Medicines and Health Products, I.P.; 2 Department of Gastroenterology and Hepatology, Hospital Santa Maria, Medical School of Lisbon; 3 Faculty of Pharmacy University of Lisbon; 4 Exigo Consultores, Lisbon, Portugal. E-mail: jorge.rodrigues@infarmed.pt

Introduction: In February 2015 the Portuguese Ministry of Health initiated an ambitious policy granting universal and national access to ledipasvir/sofosbuvir and sofosbuvir regimens for the treatment of all Portuguese patients in the national web based registry with hepatitis C. Our objective is to present, one year after the implementation of the program/strategy, for the very first time, real-world evidence on sustained virologic response (SVR) rates in a cohort including over a thousand of patients.

Material and Methods: Hepatitis C patient demographics and history of liver disease (diagnosis, genotype, METAVIR fibrosis score) and other clinical data (HIV coinfection, naïve or treatment experienced) were registered at cohort entry. Treatment options and duration, as well as clinical and virologic data were collected throughout treatment and posttreatment follow-up. An SVR was defined as undetectable HCV RNA at 12 (SVR12) and 24 (SVR24) weeks after treatment completion. Chi-square and Fisher exact tests were used and 0.05 significance level was adopted.

Results: One year after of the to new generation direct-acting antivirals 8,856 treatments were authorized and 5,449 patients has had initiated their treatment. Of those, 94% were treated with ledipasvir/sofosbuvir (Table) and 1,069 have information about SVR12 and SVR24. The average age of patients is 51.6 years-old and more than half have advanced fibrosis F3/F4, 54.4% (582/1,069). The overall SVR rate was 96.3%: HCV genotype G1 97.2%; G2 94.1%; G3 90.3%; G4 94.7%. Female were more likely to present SVR (98.7% vs 95.3%, p-value = 0.01). The probability of SVR was significantly lower in cirrhotic when compared to non-cirrhotic patients (91.6% vs 98.2%, p-value < 0.0001). The presence of cirrhosis has a more pronounced decrease in the probability of SVR in men (risk ratio = 0.92; 95%CI: 0.88 to 0.96, p-value < 0.0001) than in women (risk ratio = 0.97; 95%CI: 0.93 to 1.01, p-value = 0.07). HCV genotype 3 patients with cirrhosis and past treatment experience had 86.1% of SVR. HIV coinfection status (positive 97.1% vs negative 96.1%, p-value = 0.58) or by treatment experience (naïve 97.1% vs experienced 95.6%, p-value = 0.29).

Conclusion: Real-life data demonstrates that hepatitis C treatment with universal access to ledipasvir/sofosbuvir and sofosbuvir is associated with very high SVR, >95% irrespective of HCV genotype involved. The most difficult patients to treat are those with G3 and cirrhosis.
**SIX WEEKS OF SOFOSBUVIR/LEDIPASVIR (SOF/LDV) ARE SUFFICIENT TO TREAT ACUTE HEPATITIS C VIRUS GENOTYPE 1 MONOINFECTION: THE HEPNET ACUTE HCV IV STUDY**

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abstract Number</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Abstract Body</th>
</tr>
</thead>
</table>

Morgan Stanley
Background and Aims: The use of the new combinations of Direct Acting Antivirals (DAAs) in chronic hepatitis C virus (HCV) infection allows a sustained virological response (SVR) in more than 90% of cases. Strategy of retreatment after a prior DAAs-based regimen failure is still unclear. Methods: We identified patients who underwent DAAs-based antiHCV retreatment among those who were given DAAs from September 2013 to September 2015. A SVR was defined as undetectable HCV RNA 12 weeks after treatment completion. Results: SVR rates were available for 447 patients. 50/447 (11.1%) patients had a first virological failure with DAAs: 24 (45% were male and 79% had cirrhosis) had been empirically retreated. The genotypes were G1/G2/G3/G4 for respectively 12/2/4/6 retreated patients. All these patients were exposed to sofosbuvir (SOF) during the first and second treatment by DAAs combination. Patients were retreated with combination of SOF + ledipasvir (LDV) or SOF + daclatasvir (DCV) or SOF + simeprevir (SMV) or SOF + pegylated-interferon (PEG) ± ribavirin (RBV) during 12 or 24 weeks (retreatments are detailed in Table 1). 20 of the 24 retreated patients achieved the 12-weeks after treatment completion follow-up. All the 20 retreated patients achieved a SVR. Evaluation of baseline viral polymorphism is in progress. Conclusions: Failures to Sofosbuvir-including regimen are 2-fold higher in the real-life than in phase 3 trials. The high SVR rate after retreatment by DAAs using sofosbuvir according to the empirical EASL recommendation is promising. The optimal strategy based on the virological resistance analysis had to be defined.
EFFECT OF SOFOSBUVIR/DACLATASVIR +/- RIBAVIRIN ON THE PHARMACOKINETICS OF CALCINEURIN INHIBITORS IN LIVER TRANSPLANT RECIPIENTS – FROM THE ANRS CO23 CUPILT STUDY

**Company**
Gilead

**Drug**
Sofosbuvir

**Abstract Number**
FRI-212

**Abstract Body**
Background and Aims: The use of direct acting antivirals (DAA) has dramatically improved efficacy to treat hepatitis C virus (HCV) recurrence after liver transplantation. Although safety profile is good, reports of drug-drug interactions in real-life between calcineurin inhibitors and DAA remain limited. We describe the effect of sofosbuvir (SOF)-daclatasvir (DCV) on disposition of tacrolimus (TAC) and cyclosporine (CyA). Methods: Liver transplant patients (pts) with HCV recurrence who signed the informed consent were included in the ANRS CO23 CUPILT cohort and their characteristics recorded. Herein, we selected pts treated with SOF and DCV ± ribavirin (RBV) at standard dose. Immunosuppressive therapy backbone was either TAC or CyA. Predose blood samples were drawn before DAA initiation (D0) and at week 4 (W4) after DAA initiation. Trough concentrations (Ct) of TAC or CyA at steady state were measured by quality controls validated assays (immunoassay or LC-MS/MS). Apparent clearance (Cl/F) of TAC or CyA was estimated from the ratio of the dose per intake over the Ct (as a surrogate of mean concentration at steady state) and the time interval between 2 doses Cl/F = D/(Dt*Ct). W4/D0 geometric mean ratio (GMR) and 2-sided 90% confidence intervals (CI90) were calculated for Cl/F and compared to the 0.80–1.25 bioequivalence range. Other results are medians and ranges. Results: Twenty two pts were on TAC, among them 10 pts received SOF/DCV and 12 received SOF/DCV/RBV. Among eight pts on CyA, 7 received SOF/DCV/RBV and one received SOF/DCV. Characteristics at inclusion were: 58 year 43–81, weight 71 kg [45–106] and MELD score 8 [0–19]. HCV genotypes were G1 (23 pts), G3 (2 pts) and G4 (5 pts). Among 3 HIV+/HCV+ pts antiretrovirals were as follows: efavirenz- (EFV) (n = 1) and raltegravir- (n = 2) based regimen combined with 2 nucleoside analogs. The highest TAC Cl/F was observed in the patient treated by EFV. Creatinine clearance (MDRD equation) remained unchanged at W4 compared to D0. Cl/F of CyA remained unchanged (GMR = 1.05 and CI90 (0.84–1.30)) for the 7 pts on SOF/DCV/RBV. A significantly increase of TAC Cl/F was observed in patients SOF/DCV/RBV in comparison with the SOF/DCV group: the GMR (CI90) was evaluated to 1.69 [1.20–2.38] and 1.16 [0.85–1.60], respectively. Conclusions: Our data show that liver recipients treated by SOF/ DCV ± RBV should be monitored closely at the time of DAA initiation and during follow-up. The identification of factors explaining the DAA-TAC interaction observed is ongoing.
Background and Aims: HCV-recurrence after liver transplantation used to be a hard and sad issue in the era of interferon-based treatment. Since the introduction of modern direct acting antivirals, treatment became easier and shorter. According to published data, antiviral treatment duration with sofosbuvir (SOF) and ledipasvir (LDV) may be shortened to 12 instead of 24 weeks using ribavirin (RBV) additionally in the natural course of hepatitisC-infection. Furthermore, the question, if ribavirin is really necessary in a 12-week SOF/LDV-treatment in transplant setting, is still unanswered. Methods: 98 liver transplant patients with HCV-recurrence underwent interferon-free sofosbuvir-based treatment at our institution. 23 genotype 1 or 4 patients were treated with SOF/LDV for 12 weeks in case of histologically proven stage 0–2 fibrosis and 21 patients either received SOF/LDV plus weight adjusted ribavirin (RBV) or prolonged treatment for 24 weeks in case of advanced fibrosis stages (F3–4). Results: End of treatment response (ETR) was achieved in 100% in both groups in 43 patients, sustained virological response (SVR) was achieved currently in 100% in 35 patients, while 8 patients are still under observation and one is on treatment. Patients with prolonged treatment duration or with RBV developed significantly more adverse events compared to the SOF/LDV-group 16 (76.2%) vs. 6 (26.1%) p = 0.002. One of the dominant and most relevant adverse events was the development of anemia in 55.6% of 18 patients receiving RBV, which was significant (p < 0.001). RBV-comedication had to be reduced in 11 (61.1%) and then stopped in 8 (44.4%) patients due to adverse events. No significant difference was observed among the groups regarding kidney function. Conclusions: SOF/LDV-combination is a reliable therapy of recurrent HCV-infection after liver transplantation. It is easy to administer and to achieve SVR in immunocompromised patients without interactions with the immunosuppressive medication. Regarding the high rate of adverse events, RBV-treatment discontinuation and 100% > SVR in patients with advanced fibrosis stages, there is no need for RBV as comedication in the SOF/LDV-regimen.
Background and Aims: Direct-acting antivirals (DAA) are revolutionizing HCV therapy (Tx) in liver transplant (LT) setting. In this study we aimed to identify factors associated with sustained virologic response at week 12 post Tx (SVR12) and survival (composite endpoint) among LT patients (pts) treated with a sofosbuvir (SOF)-based regimen. Methods: Since July 2014 to May 2015, we enrolled 127 pts transplanted in Turin Centre and affected by hepatitis C recurrence, fibrosis stage 3 (35 pts) or 4 (92 pts), according to Metavir. Median follow-up since start of antiviral Tx 14.5 months (range 6.3–16.3). Median age 61 years (44–75), BMI 24.6 (16.4-34.4). Median donor age 60 years (22–85). Immunosuppression was based on cyclosporine (CyA), 43% or tacrolimus (Tac), 42% and/or mycophenolate (MMF), 44%. IL28B CC 24%, HLA DRB1*11 positive phenotype 28%. GT173% (1a 13%), GT2 5%, GT3 17%, GT4 5%; 65% experienced to previous Tx. Median time LT-Tx 52.8 months (3.3-174.2). Median baseline HCVRNA 6.4 Log IU/mL (3.9–7.9). Median eGFR 72 mL/min (32–139) with CKD-EPI estimating equation. In cirrhotic group the median MELD and Child were 10 (6–22) and 6 (5–12), respectively. According to Italian DAA availability, 118 pts received SOF 400 mg/day + weight-based ribavirin (RBV) for 24 weeks and 9 pts (2 GT1a and 7 GT1b) SOF + Simeprevir 150 mg/day + RBV for 12 weeks. Results: All 35 pts with stage 3 fibrosis achieved SVR12 and are alive. In cirrhotic group, 2 patients died on Tx and 3 after the end of Tx (on day 41, 143 and 169), due to end stage liver disease and SVR12 rate was 76% (70/92), according to intention to treat analysis. The 19 relapers were: 90% GT1, 26% IL28B CC, all treated with SOF + RBV; 58% HCVRNA negative at week 4 on Tx; baseline median MELD 12 (6–20), Child 7 (5–12), eGFR 77 mL/min (32–111). SVR12 rate was significantly higher in cirrhotic pts tolerating ≥80% of full weight-based RBV dose compared with ones tolerating <80% of the dose (82% vs 53%, p = 0.01).

Fig. 1 shows as in the cirrhotic group at the univariate analysis, MELD < 11 and Child <B7 were the only statistically significant predictors of the composite endpoint (SVR12 + alive). None discontinued antiviral therapy due to adverse events, and 10% underwent blood transfusion due to RBV-related anemia. Conclusions: SOF-based antiviral Tx was well tolerated in pts affected by mild-severe HCV recurrence after LT. MELD < 11 and Child <B7 in cirrhotic pts and fibrosis stage 3 predicted the composite endpoint of viral eradication + survival.
Background and Aims: The treatments of hepatitis C in liver transplant patients until recently, had low efficacy and many adverse effects. The new direct acting antivirals Simeprevir(SIM) and sofosbuvir(SOF) have significantly increased the efficacy and safety of treatment in liver transplant hepatitis C patients genotype 1. The aim of this study was to determine the efficacy and safety in real life of the combination SOF + SIM ± RBV in a group of liver transplant patients genotype 1. Methods: This is a multicenter, retrospective study including 232 genotype 1 hepatitis C liver transplant patients treated with SIM + SOF ± RBV from 21 Liver transplant Centres. Efficacy and safety data, and mortality rate were assessed. Results: The majority of patients were male(73.7%) and the average age was 61.49 ± 8.9 years. The 63.1% were Ile 28B CT and the genotype 1a was 15.02%. The 59.05% of patients have been previously treated, the most part with interferon based therapy, but 10.8% with IP and the 4.3% with SOF. The 51.14% were null responders. There was a 53.8% of patients with fibrosis 4. The MELD score average was 8.86 ± 2.87(6–24). In the 60.34% of the patients RBV was included in the treatment. The majority of the patients were treated during 12 weeks(86.63%). At the end of treatment(EOT), all patients had undetectable serum HCV-RNA but one patient had to stop the treatment for liver and kidney impairment. The rates of sustained virological response(SVR) 4 and 12 were 97.28% and 93.75%, respectively. The SVR 12 in cirrhotic patients was 92.4% versus 95.34 in non cirrhotics, and SVR 12 in RBV treated patients was 95.7% versus 90.9%. Treatment was well tolerated and the mortality rate was 1.3% no treatment related Conclusions: The treatment of HCV genotype 1 patients after liver transplantation, with Simeprevir plus sofosbuvir in real life, is a very effective and safe option even in post-transplant liver cirrhosis The mortality rate was very low and no drug-related.
EFFICACY AND SAFETY OF SIMEPREVIR AND SOFOSBUVIR WITH AND WITHOUT RIBAVIRIN FOR 12 WEEKS IN SUBJECTS WITH RECURRENT GENOTYPE 1 HEPATITIS C POST-ORTHOtopic LIVER TRANSPLANT: THE GALAXY STUDY

**Company**
Gilead

**Drug**
Sofosbuvir

**Abstract Number**
FRI-457

**Abstract Body**

Background and Aims: Simeprevir (SMV) is a hepatitis C virus (HCV) protease inhibitor approved as part of a combination antiviral regimen to treat non-transplant patients with chronic hepatitis C genotype 1 infection. Methods: This is an ongoing, prospective, partially-randomised, phase 2, open-label study of once-daily SMV 150 mg + sofosbuvir (SOF; HCV nucleotide polymerase inhibitor) 400 mg with and without ribavirin (RBV) 1000 mg (1200 mg for subjects ≥75 kg) in subjects with recurrent genotype 1 HCV post-orthotopic liver transplant; the primary endpoint was the proportion of subjects with wk 12 sustained virologic response (SVR12). Choice of immunosuppression was at the investigator’s discretion, excluding cyclosporine due to the drug interaction with SMV. The first 33 subjects without cirrhosis were randomised 1:1:1 into three arms and stratified by genotype subtype and presence of Q80K: 1) SMV + SOF + RBV ×12 wks, 2) SMV + SOF ×12 wks, and 3) SMV + SOF ×24 wks; 13 additional subjects (2 with, 11 without cirrhosis) were enrolled in the SMV + SOF 24-wk arm. An interim analysis was performed when all subjects in the 12-wk arms reached the SVR12 timepoint. The final analysis (including pharmacokinetics) will be presented at the congress.

Results: All 46 subjects received at least one dose of study drug; median age, 60 y; 74% male; 80% white; mean (standard deviation) baseline HCV RNA level, 6.4 (0.8) log10 IU/mL; 72% genotype 1a (three subjects/arm had Q80K). Median time since liver transplant was 4.5 y. At the time of analysis, five subjects in the 24-wk arm (without cirrhosis) and 22 subjects in the 12-wk arms had reached the SVR12 timepoint; 93% (25/27) achieved SVR12 (82% in RBV arm and 100% in arms without RBV). Two subjects did not achieve SVR12 (one had viral relapse at follow-up wk 4, one did not have wk 12 data [death by suicide]; both were in the RBV arm). Four (9%) subjects had a serious adverse event, considered unrelated to treatment per investigator. No episodes of acute rejection were reported. Conclusions: In liver transplant recipients with recurrent HCV infection, SMV + SOF treatment for 12–24 wks with or without RBV resulted in a high SVR12 rate (93%) and was well tolerated; SVR12 was achieved by 100% of subjects with available data in both SMV + SOF arms without ribavirin, suggesting that 12 wks of SMV + SOF therapy is adequate for genotype 1 liver transplant subjects without cirrhosis.
Background and Aims: Sofosbuvir/Ribavirin-based regimens (SOF/R) prevent HCV graft reinfection in listed patients with HCV-RNA undetectability 4 weeks before liver transplant (LT). SOF/R-induced HCV clearance could also improve liver function in listed patients resulting in a possible delisting for clinical improvement while also reducing list drop-out due to disease progression. The aim was to investigate in listed cirrhotic patients the effect of HCV clearance on liver disease severity before transplant and the rate of SOF-induced prevention of HCV graft reinfection. Methods: From June 2014 to September 2015, 35 patients listed for HCV-related cirrhosis ± HCC received SOF/R until transplant or for 48 weeks. Clinical-laboratory tests and liver stiffness by transient elastography (TE) were sequentially assessed and compared with histology of native liver, blindly reviewed by two pathologists who subclassified cirrhosis (F4) by Laennec (4A,B,C) according to histological severity. Results: 25 patients (71%) were transplanted. Among them, 18 (72%) were HCV-RNA(−) for >4 weeks and stopped SOF/R, while 7 (28%) with suboptimal viral response extended treatment post-transplant for 24 weeks. Median treatment duration was 4 months (range 1–10); waiting list 4 months (1–8) and post-transplant follow-up 8 months (2–14). Most patients had GT-1 (60%), 64% HCC, HCV-RNA median values were 5 log10 UI/mL (2-7), MELD 11 (7–25) CPT 10 (5– 14), esophageal varices detected in 16 (64%) cases, ascites in 16 (64%), encephalopathy in 12 (48%). TE baseline value was 34 Kpa (14–75). LT candidates who were classified as decompensated (Child 7–14, n = 16) and compensated cirrhotics (n = 9) significantly differed for MELD score (16 vs 9, p < 0.003) and HCV-RNA levels (5 vs 6 log10, p = 0.05). Liver stiffness value did not improve during therapy in decompensated patients (34 vs 36 Kpa, p = 0.75) who showed more advanced stages of cirrhosis by Laennec (4B-C = 100%). In contrast, liver stiffness significantly decreased in compensated patients (31 vs 22 Kpa, p = 0.04) and 5 patients (56%) resulted as Laennec stage 4A. SVR12 was achieved in 92% of overall treated recipients. Conclusions: Liver stiffness did not improve during anti-HCV treatment in decompensated cirrhotics on waiting list and was associated with more advanced histological stages of cirrhosis at transplant. Effective prevention of HCV graft reinfection by SOF/R was achieved in the large majority of listed patients.
Background and Aims: The introduction of direct antiviral agents (DAAs) has radically changed the treatment of recurrent HCV infection after liver transplantation (LT), allowing to reach sustained virological response (SVR) rates much more often that with conventional peg-interferon alfa (P) and ribavirin (R) therapy and with minimal side-effects. We aimed to assess whether the clinical and functional liver changes associated with the achievement of SVR differ when this is obtained after DAA or PR. Methods: Fifteen HCV genotype-1 LT recipients (M/F 11/4, median age 56.2) who achieved SVR with sofosbuvir (S), 400 mg/day, and R (800 mg/day) therapy were compared with a matched group (M/F 9/ 6, median age 60.4) who achieved SVR after P (180 mcg/wk) and R (1000–1200 mg/die) therapy. Liver function tests and liver stiffness (transient elastometry) were assessed at baseline, 4 week, 12 week, end of treatment (EOT) and at week 24 after EOT. Portal vein main velocity was assessed at baseline, EOT and at week 24 after EOT by abdominal Doppler ultrasound scan. Results: Baseline characteristics were comparable in the two groups. Aminotransferase (ALT) showed a significantly greater decrease after SR than after PR during treatment (week 12: 30.4 ± 11.3 vs 44.5 ± 15.1 IU/L; p = 0.008) as well as at week 24 after EOT (21.2 ± 5.4 vs 26.9 ± 4.9 IU/L; p = 0.001). Liver stiffness decreased at week 24 after EOT by an average of 38% and 23% in the SR and PR group, respectively (p = 0.04) compared to baseline values. Portal vein velocity was significantly higher in the SR than in the PR group both at EOT (23.1 ± 2.3 vs 19.7 ± 2.9 cm/sec and at week 24 after EOT (23.4 ± 2.8 vs 20.3 ± 1.6 cm/sec; p < 0.001). Conclusions: In patients who obtain SVR, SR therapy determines an earlier and greater on-treatment improvement of liver function and portal hemodynamics compared to PR therapy. Achievement of SVR24 is associated with significantly lower ALT levels (to below the normal values), lower liver stiffness and higher portal blood velocity following SR compared to PR therapy. Whether these differences are long-lasting and reflect distinct mechanisms of action of S (inhibition of viral replication) vs P (immune-stimulatory effect) requires further studies.
FAILURE TO RESPOND TO SOFOSBUVIR AND RIBAVIRIN AFTER LIVER TRANSPLANTATION

Company: Gilead

Drug: Sofosbuvir

Abstract Number: FRI-479

Abstract Body: Background and Aims: Predictors of failure of combined therapy with sofosbuvir (SOF) and ribavirin (RIBA) in liver transplant (LT) recipients affected with recurrent hepatitis C virus (HCV) are largely unknown. Methods: This was a retrospective analysis of adult, maintenance LT recipients enrolled in the SOF compassionate program at a single center. Patients were included into current analysis if: adult (≥18 years), F3-F4 at baseline, and receiving at least one dose of SOF + RIBA. Primary endpoint was treatment efficacy as end of treatment (EOT), and sustained viral responses at 4 (SVR4) and 12 weeks (SVR12). The secondary endpoint was identification of predictors of SVR12 among all clinical variables retrieved with medical record review. Results: Among 176 LT recipients enrolled in the compassionate program, 163 (males 83.5%; median age [range] 58 [30–75]) were treated with a 24-week course of SOF + RIBA and included into current analysis. Treatment was initiated at a median of 38 months [30–75] after transplantation. At baseline, mean (SD) fibrosis was 15.7 (7.8) KPa; mean (SD) HCV RNA was 1,145,288.7 (2,073,664.1) IU/mL, and genotype (GT) 1-4 was present in 123 (75.5%) cases. Child-Pugh (C-P) status was B/C in 30 (18.4%) and A in 133 (81.6%), and mean (SD) MELD score was 16.2 (3.6). Six (3.0%) patients were affected with post-transplant fibrosing cholestatic hepatitis. One-hundred-sixty-two (99.4%) patients completed the 24-week treatment course, and EOT, SVR4 and SVR12 were 100% (163/163), 85.2% (138/162), and 83.3% (135/162), respectively. The only variable associated with SVR12 was baseline serum albumin ($r = 0.41; p = 0.0001$), while total bilirubin ($r = -0.04; p = 0.78$), INR ($r = -0.13; p = 0.25$), serum creatinine ($r = 0.17; p = 0.12$), C-P status (chi-square = 1.41; $p = 0.23$), MELD ($r = -0.12; p = 0.24$), and severity of fibrosis ($r = -0.19; p = 0.11$) were not significantly associated. Conclusions: Our experience suggests that failure to respond to a combined regimen with SOF + RIBA is associated with lower serum albumin levels in LT recipients with recurrent HCV graft disease.
Background and Aims: The aim of the present study was to evaluate renal function during and after direct acting antivirals for the treatment of hepatitis C (DAA) in liver transplant patients. Methods: The study population included 193 (147 M/46 W) patients, aged 58.7 ± 9.0 years, BMI 24.2 ± 4.2 kg/m². Sofosbuvir (SOF) + ribavirine (RBV) were prescribed in 17.6% or SOF + daclatasvir (49%) or SOF + daclatasvir + RBV (33.3%). A renal dysfunction (RD) was defined according to the stage 1 RIFLE criteria: decrease of 25% of the glomerular filtration rate (GFR) estimated on MDRD formula. Dual liver-kidney transplant and patients with renal dialysis before DAA were excluded. Results: Liver fibrosis stage was F0-F2 in 35.2%, F3 in 21.2%, F4 in 30.6%, and fibrosing cholestatic hepatitis in 13%. Viral genotypes were: G1: 76.6%, G2: 2.6%, G3: 12%, G4: 8.9%. A previous treatment had been tempted in 46.6% (IFN PEG + RBV: 37.3%, IFN PEG + RBV + Boce/telaprevir: 7.8%, other 1.5%). Ciclosporine, tacrolimus, everolimus, mycophenolate mofetil was used in 29.5%, 59.1%, 7.8% an 48.7% respectively. High blood pressure was present in 50.8%, type 2 diabetes in 36.8%, a cardio-vascular disease in 21.2%, a renal disease in 26.9%. Mean duration between liver transplantation and initiation of DAA was 73.8 ± 71.9 months. The overall SVR rate at 12 weeks was 97.4%. RD was seen in 38% of patients. 31% patients had a RD after the beginning of DAA treatment, including 12% patients with a persistent RD after the end of therapy and 10% with a RD at the last visit of the follow-up. 7% patients presented a RD not during the treatment with DAA but after the end of the DAA treatment including 5% with a persistent RD at the last visit of follow-up. The presence of a preexisting renal disease (OR = 3.49 [1.57-7.75], p = 0.002), the baseline GFR (OR = 1.02 [1.01-1.04], p = 0.0006), a tacrolimus based treatment (OR = 0.43 [0.23-0.81], p = 0.01) were the predictive factors of RD. Baseline GFR (OR = 1.03 [1.01-1.05], p = 0.003), presence of a preexisting renal disease (OR = 4.19 [1.33-13.22], p = 0.014), total bilirubin (OR = 1.01 [1.00-1.02], p = 0.013) were independently associated with a persistent RD at the last visit of follow-up. Ribavirin or daclatasvir use, and metabolic factors had no impact on the occurrence of RD. Conclusions: In our large cohort, 38% of patients had a 25% decreased of GFR during or after DAA treatment; 15 % of patients kept this RD at the end of the follow-up. A renal disease before DAA treatment and the baseline GFR were the two main risk factors.
Background and Aims: HCV infection is associated with lower patient (pt) survival following combined liver kidney transplantation (CLKT). There are some concerns on renal function in liver transplant (LT) pts treated with second generation direct acting antivirals (DAAs). Study aims were to assess efficacy and tolerance of sofosbuvir (SOF)-based regimen in this difficult-to-treat population. Methods: The ANRS CO23 CUPILT study is a prospective cohort including 683 pts with HCV-recurrence following LT treated with second generation DAAs. The present work focused on 20 pts treated for HCV recurrence after CLKT. Treatment regimens were prescribed at investigator’s discretion. Pts were followed at BL, W12, W24, end of therapy (EOT), follow up W12 (FU12). Results: The study population included 20 (15M/5W) pts, aged 57.5 yrs, median BMI 22.3 kg/m2. CLKT were performed for dialyzed pts in 32% and in LT candidates with chronic renal dysfunction in 68%. At baseline, liver fibrosis stage was F0-F2 in 45%, F3 in 15%, F4 in 25%, and fibrosing cholestatic hepatitis in 15%. Viral genotypes were as follows: G1: 70%, G3: 20%, G4: 10%. Ciclosporine, tacrolimus, and mycophenolate mofetil were used in 40%, 55% and 45% respectively. Median duration between CLKT and initiation of DAA was 58.7 months. At baseline, HCV viral load, bilirubin level and glomerular filtration rate (GFR) (MDRD formula) were 6.4 log10 IU/mL, 13.8 μmol/L and 50.9 mL/min, respectively. In combination with SOF, patients received daclatasvir (DCV) (40%), DCV + RBV (15%), RBV (15%), ledipasvir (LDV) (10%), LDV + RBV (10%), PEG IFN + RBV (5%) or simeprevir (5%). Median duration of therapy was 23.9 weeks. In terms of efficacy, at W4, a complete virological response was obtained in 13/19 (68.4%) pts. Among 20 pts who have completed the treatment, the EOT response was achieved in 100%. At time of analysis 19/19 (100%) pts achieved SVR12. In terms of tolerance, GFR decreased significantly from baseline value 50.9 mL/min to 41.8 mL/min at W12 (p < 0.0001), 41.4 mL/min at EOT (p = 0.0001) and to 42.7 at FU12 (p = 0.0001). 45% of pts presented, at least, one serious adverse event. Blood transfusion and EPO were required in 20% and 45% respectively. No pts experienced acute rejection during therapy and there were no deaths during the follow up. Conclusions: SOF-based-regimen showed excellent results in terms of efficacy in difficult to treat CLKT pts. However, GFR significantly decreased during and after DAA therapy. Intensive renal function monitoring should be done in those pts.
### Abstract Body

C-EDGE HEAD-TO-HEAD: EFFICACY AND SAFETY OF ELBASVIR AND GRAZOPREVIR COMPARED WITH SOFOSBUVIR/PEGYLATED INTERFERON/RIBAVIRIN: A PHASE 3 RANDOMIZED CONTROLLED TRIAL

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
</tbody>
</table>
HIGH EFFICACY OF SOFOSBUVIR/VELPATASVIR PLUS GS-9857 FOR 12 WEEKS IN TREATMENT-EXPERIENCED GENOTYPE 1-6 HCV-INFECTED PATIENTS, INCLUDING THOSE PREVIOUSLY TREATED WITH DIRECT-ACTING ANTIVIRALS

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
</tbody>
</table>

Abstract Number

Abstract Body
## DRUG-DRUG INTERACTION PROFILE OF SOFOSBUVIR/VELPATASVIR FIXED-DOSE COMBINATION

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>FRI-168</td>
</tr>
</tbody>
</table>

### Abstract Body
Background and Aims: Sofosbuvir (SOF), a nucleotide analog NS5B inhibitor, and velpatasvir (VEL), a pangenotypic NS5A inhibitor, are being developed for the treatment of chronic HCV infection. The drug-drug interaction (DDI) profile of SOF/VEL was characterized using in vitro data, Phase 1 clinical data, and population PK data from Phase 2/3 studies.

Methods: The Phase 1 program evaluated DDIs between SOF/VEL or its components and HIV antiretrovirals (ARVs), oral contraceptives (OCs), acid-reducing agents, immunosuppressants, opiates, and drug transporter and CYP probes. The effect of concomitant medications used in Phase 2/3 studies on SOF/VEL PK was also assessed by population PK analyses.

Results: No clinically relevant changes in atazanavir (ATV)/ritonavir (r), cobicistat, darunavir/r, dolutegravir, efavirenz (EFV), elvitegravir, emtricitabine, lopinavir/r, raltegravir, rilpivirine, or tenofovir alafenamide (TAF) PK were seen when coadministered with SOF/VEL. SOF/VEL increased tenofovir (TFV) exposure (~40 to 81%) when administered as TDF, but not as TAF. No clinically relevant changes in SOF or GS-331007 (primary circulating metabolite) PK were observed with ARVs. Efavirenz decreased VEL AUC 53% and ATV/r increased VEL AUC 142%. A small increase in ethinyl estradiol (EE) Cmax (39%) and decrease in Ctau (17%) with no change in AUC occurred when representative OC EE/norgestimate was administered with VEL; norgestrel AUC and Ctau increased (19% and 23%) when was administered with SOF. Histamine-2 receptor antagonists (famotidine 40 mg BID) did not impact SOF/VEL exposure. Omeprazole (OME) 20 mg resulted in a decrease in VEL AUC (26–38%) and no impact on SOF or GS-331007 AUC when given with food. Larger decreases in VEL AUC were observed with OME 40 mg (56%) or when administered under fasting conditions (36–57%). Sofosbuvir and VEL AUC decreased 72% and 82%, respectively, when coadministered with rifampin, a potent P-gp and CYP inducer. Pravastatin and rosuvastatin AUC increased 35% and 169%, respectively, when coadministered with VEL. A small increase in digoxin AUC (34%) was observed with VEL. No clinically relevant interactions were observed upon administration of VEL with CsA or SOF with CsA, TAC, or methadone. Anticoagulants, SSRIs, calcium channel blockers, statins, diuretics, or rifaximin did not affect SOF/VEL PK in Phase 2/3 studies. Conclusions: SOF/VEL exhibits a favorable DDI profile allowing use with various drugs commonly used by HCV-infected patients.
### STEADY-STATE PHARMACOKINETICS OF SOFOSBUVIR AND VELPATASVIR IN HCV-INFECTED SUBJECTS WITHOUT CIRRHOSIS, WITH COMPENSATED CIRRHOSIS, OR WITH DECOMPENSATED CIRRHOSIS IN THE PHASE 3 ASTRAL STUDIES

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>FRI-169</td>
</tr>
</tbody>
</table>

#### Abstract Body

**Background and Aims:** The Phase 3 ASTRAL studies evaluated a fixed-dose combination of sofosbuvir (SOF), a nucleotide analog HCV NS5B inhibitor, and velpatasvir (VEL), a pangenotypic HCV NS5A inhibitor, for the treatment of chronic HCV infection. This analysis describes the steady-state pharmacokinetics (PK) of SOF, SOF metabolites, and VEL in HCV-infected patients without cirrhosis, with compensated cirrhosis, and with decompensated cirrhosis. Methods: Patients enrolled in the ASTRAL-1 and ASTRAL-4 studies who consented to participate in a PK substudy had serial plasma sample drawn over a period of 24 hours at the Week 2 or Week 4 on-treatment visit. Study drug administration times were recorded for the week preceding serial PK draws. Plasma concentration of SOF, SOF metabolites, and VEL were quantified by LC/MS/MS. ASTRAL-1 patients received SOF/VEL 400/100 mg once-daily and ASTRAL-4 patients were randomized to receive SOF/VEL 400/100 mg once-daily ± ribavirin (RBV). Results: Sixty-nine subjects without cirrhosis or with compensated cirrhosis in ASTRAL-1 had evaluable serial PK data. Thirty-three subjects with decompensated cirrhosis in ASTRAL-4 had evaluable serial PK data; 27 receiving SOF/VEL and 6 receiving SOF/VEL + RBV. Subjects with decompensated cirrhosis resulted in VEL AUCtau that was 7% (with RBV) to 14% (no RBV) lower than subjects without cirrhosis and those with compensated cirrhosis. Velpatasvir Cmax was modestly lower (27% to 41%) and Ctau was modestly higher (41% to 54%) in subjects with decompensated cirrhosis compared to those without cirrhosis and those with compensated cirrhosis. Sofosbuvir AUCtau and Cmax were higher (90% to 106% and 30 to 37%, respectively) in subjects with decompensated cirrhosis. GS–331007 (primary circulating SOF metabolite) exposures were similar in subjects regardless of hepatic function. The differences in SOF and VEL PK were consistent with those observed in dedicated Phase 1 studies evaluating the PK of SOF and VEL in HCV-uninfected subjects with mild, moderate, or severe hepatic impairment compared to healthy subjects. Conclusions: Modest differences in the PK of SOF and VEL were observed in HCV-infected subjects with decompensated cirrhosis versus those without cirrhosis or with compensated cirrhosis. Results are consistent with previously observed SOF and VEL PK in populations with hepatic impairment and are not expected to be clinically meaningful.
# NEXT-GENERATION SEQUENCING ANALYSIS OF NS5A AND NS5B MINOR RESISTANCE-ASSOCIATED VARIANTS IN PATIENTS WITH HCV GENOTYPE 3 INFECTION WHO FAILED TREATMENT WITH DACLATASVIR PLUS SOFOSBUVIR

**Company**
Gilead

**Drug**
Sofosbuvir

**Abstract Number**
FRI-171

**Abstract Body**
Background and Aims: The ALLY-3 phase 3 study assessed the efficacy of 12 weeks of daclatasvir (pangenotypic NS5A inhibitor) + sofosbuvir (NS5B nucleotide inhibitor) in patients with HCV GT 3 infection. The majority (89%) of these patients achieved a sustained virologic response. Of the 17 patients who failed treatment, emergent variants in the HCV NS5A region at L31I, S62L, and Y93H were observed. Here, the presence of minor variants in the HCV NS5A and NS5B regions at baseline and at failure were assessed in the 17 patients who failed treatment in the ALLY-3 study using next-generation sequencing. Methods: Plasma samples were analysed using next-generation sequencing (Illumina technology; sensitivity ≥1% [DDL, Netherlands]). The HCV NS5A (amino acids 28, 30, 31, and 93) and NS5B (amino acids 159, 282, and 321) regions were surveyed and the results compared with those obtained using direct sequencing (sensitivity cut-off ~20%). Results: Using next-generation sequencing, minor variants in the HCV NS5A region at M28, A30, or Y93 were observed in three patients. M28V (1.3%) or A30V (1.6%) were no longer detected at relapse in two patients with these respective variants at baseline, while the minor variant Y93H (2%) observed in one patient was enriched (99.4%) at failure. No minor variants associated with resistance to sofosbuvir were observed, including the two patients who had also failed prior treatment with sofosbuvir. At treatment failure, the only detected signature variants in NS5A were A30K (one patient), L31I (one patient) and Y93H (15 patients; eight were emergent). All of these variants were also detected by direct sequencing. One patient had emergent NS5B S282T together with emergent NS5AY93H at treatment failure; neither variant was detected at baseline or by post-treatment Week 12 using next-generation sequencing. Conclusions: In general, minor variants in NS5A (at 28, 30, 31, or 93) and NS5B (at 159, 282, or 321) were not detected at baseline by next-generation sequencing in patients with emergent variants associated with resistance to daclatasvir or sofosbuvir. In trying to determine which patients with HCV GT 3 infection would respond to treatment with 12 weeks of daclatasvir + sofosbuvir, next-generation sequencing delivered similar results to those obtained using direct sequencing. From these data, the presence of minor variants in NS5A or NS5B at baseline does not appear to predict response to treatment with daclatasvir + sofosbuvir.
IMPRESSIVE GAINS IN PATIENT-REPORTED OUTCOMES ARE OBSERVED IN CHRONIC HEPATITIS C PATIENTS WITH OR WITHOUT CIRRHOSIS WHO ARE TREATED WITH SOFOSBUVIR AND VELPATASVIR: RESULTS FROM ASTRAL-1, -2, -3 AND-4

Company  Gilead
Drug  Sofosbuvir

Abstract Number  FRI-200

Abstract Body  Background and Aims: Patients with HCV and cirrhosis report significant impairment of patient-reported outcomes (PROs) such as health-related quality of life and fatigue. Our aim was to compare the effect of sofosbuvir and velpatasvir (SOF/VEL) on PROs in HCV patients with and without cirrhosis. Methods: Efficacy, safety and patient-reported outcomes (SF-36, CLDQ-HCV, FACIT-F, WPAI:HCV) were assessed in four prospectively designed phase 3 clinical trials of SOF/VEL (ASTRAL-1 through ASTRAL-4). The baseline PROs and treatment-emergent changes in PRO scores were compared between patients with and without cirrhosis who were treated with SOF/VEL. Results: A total of 1,213 patients received SOF/VEL for 12 or 24 weeks: 813 without cirrhosis and 400 with cirrhosis. Patients with cirrhosis were older, more frequently male, had lower employment rate, as well as more pre-treatment anxiety, fatigue and type 2 diabetes (all p < 0.05). At baseline, patients with cirrhosis also had significantly lower PRO scores (up to −18.9 points on a universal 0–100 scale, p < 0.05 for 21 out of 25 studied PROs). In multivariate analysis, adjusted for demographics and clinical factors at baseline, having cirrhosis was independently associated with substantial impairment of PROs (−5.2 to −11.4 points to the summary PROs, all p < 0.05). The SVR-12 rates were 98.5% in non-cirrhotic and 91.0% in cirrhotic patients who were treated with SOF/LDV (p < 0.0001). By the end of treatment, significant improvements in PRO scores were observed in patients with cirrhosis (the average improvement across 25 PRO domains was +5.6 points, maximum +14.6, p < 0.05 for 21/25 PROs), as well as in patients without cirrhosis (average +2.6 points, maximum +9.8 points, p < 0.05 for 19/25 PROs). After 12 weeks of follow-up, these improvements remained significant in both cirrhotics (up to +14.3 points, p < 0.05 for 21/25 PROs) and noncirrhotics (up to +10.9 points, p < 0.05 for 23/25 PROs). After 24 weeks of follow-up, more improvements were noted in some PRO scores (up to +14.6 points, p < 0.0001) regardless of the presence or absence of cirrhosis. In multivariate analysis, improvements in physical health-related PROs during treatment were more substantial in cirrhotic patients than in non-cirrhotic patients (by +1.6 to +6.2 points, p < 0.05). Conclusions: Patients with and without cirrhosis experience significant improvement of their PROs during treatment with an all-oral SOF/VEL regimen and after achieving SVR.
THE LEVELS OF MONOAMINE NEUROTRANSMITTERS IN HCV PATIENTS TREATED WITH LEDIPASVIR (LDV)/SOFOSBUVIR (SOF)

Company
Gilead

Drug
Sofosbuvir

Abstract Number
FRI-201

Abstract Body
Background and Aims: The underlying cause of mood disorders in HCV is unknown. Furthermore, ribavirin (RBV)-induced neuropsychiatric side effects may affect level of neurotransmitters. We investigated alteration of serum neurotransmitters in HCV-infected patients during and post-treatment, and associated these changes with mental health abnormalities. Methods: HCV genotype 1 (GT1) patients who had achieved SVR-12 after 12 weeks of LDV/SOF ± RBV were selected (ION-1). Frozen serum samples from baseline, end of treatment (EOT), and 4 week follow-up were used to assay 16 cytokines and monoamine neurotransmitters [dopamine (pg/mL), norepinephrine (pg/mL), serotonin (ng/mL), and a serotonin amino acid precursor (tryptophan) (nmol/mL)]. A number of validated self-reports were used to assess mental and emotional health (MEH) [Emotional Domain (EM) of CLDQ-HCV, the Role Emotional (RE), Mental Health (MH), and the Emotional Well-Being (EWB) of FACIT-F].

Results: 100 GT1 HCV patients were included (age 53 years, 57% male, 17% cirrhosis). Levels of dopamine at baseline and EOT positively correlated with RE (r = 0.25, p = 0.01 and r = 0.22, p = 0.03). Four weeks after treatment, the levels of dopamine were higher in patients who had received SOF/LDV+RBV than SOF/LDV (707 ± 462 pg/mL vs. 693 ± 259 pg/mL, p = 0.03). In contrast, post-treatment the levels of serotonin were lower in patients receiving SOF/LDV+RBV as compared to SOF/LDV (112 ± 146 ng/mL vs 168 ± 136 ng/mL, p = 0.02). Serotonin levels were also found to be lower in patients with depression at all time points (all p < 0.0001). Interestingly, post treatment we noted a significant reduction in the level of serotonin in patients receiving RBV (SOF/LDV+RBV: −25 ± 131 ng/mL, p = 0.02). In multivariate analysis, baseline TNF-alfa was associated with MEH (p < 0.01). At the end of treatment, a drop in MCP-1 and IL8 were independently associated with gains in MEH (p < 0.05). Finally, post-treatment, a drop in IL8, PDGF and IL1ra were independently associated with MEH (p < 0.05). We also noted that HCV patients with a history of chronic pain had consistently lower levels of norepinephrine (p < 0.05). Additionally, there was also a significant reduction in norepinephrine after 4 weeks of post-treatment in HCV patients with chronic pain (−304.72 ± 1241.73 pg/mL, p = 0.01).

Conclusions: Alteration of monoamine neurotransmitters in HCV infected patients may be associated with MEH which can get exacerbated with RBV.
DEEP SEQUENCING RESULTS FROM THE PHASE 2 IMPACT STUDY OF SIMEPREVIR IN COMBINATION WITH DACLATASVIR AND SOFOSBUVIR IN TREATMENT-NAÏVE AND -EXPERIENCED PATIENTS WITH CHRONIC HEPATITIS C VIRUS GENOTYPE 1 OR 4 INFECTION AND DECOMPENSATED LIVER DISEASE

Company | Gilead
---|---
Drug | Sofosbuvir
Abstract Number | THU-215

Abstract Body

Background and Aims: The Phase 2, open-label IMPACT study (NCT02262728) is investigating 12 weeks of simeprevir (NS3/4A inhibitor; 150 mg once daily), daclatasvir (NS5A inhibitor; 60mg once daily) and sofosbuvir (NS5B inhibitor; 400 mg once daily) in patients with hepatitis C virus (HCV) genotype 1/4 infection and decompensated liver disease. Deep sequencing assessed the presence of pretreatment resistance-associated variants. Methods: Deep sequencing of HCV NS3, NS5A and NS5B genes was performed on the Illumina MiSeq platform (1% detection limit). In addition, population sequencing data of the same genes were available at baseline for all 40 patients (26 genotype 1a, 13 genotype 1b, 1 genotype 4). Amino acid substitutions at NS3 positions 43, 80, 122, 155, 156 and 168; NS5A positions 28, 30, 31, 32 and 93; and NS5B positions 96, 142, 159, 282, 316, 320, 321, 390 and 415 were considered. Among these, the analysis focused on resistance-associated variants defined as substitutions associated in vitro with simeprevir, daclatasvir or sofosbuvir fold change in 50% effective concentration compared with wild type >2.

Results: Deep sequencing confirmed the results from population sequencing and additional resistance-associated variants were observed with quasispecies frequencies ranging from 1–13%. By deep sequencing, 42% (16/38), 13% (5/39) and 0% (0/39) of patients carried baseline resistance-associated variants at positions of interest in NS3, NS5A and NS5B, respectively. 32% of patients carried simeprevir resistance-associated variant Q80K (12/38; all genotype 1a; all at 100% variant frequency), 11% had Q80R (4/38; 2 genotype 1a, 2 genotype 1b; variant frequency 1–99%) and 3% had F43L (1/38; genotype 1a; variant frequency 13%). Daclatasvir resistance-associated variant Y93H was observed in 10% (4/39; all genotype 1b; variant frequency 1–98%) of patients; Q30R and Y93C were seen in 1 patient each (3%; in a 1a and 1b patient, at 1% and 4% variant frequency, respectively). All patients carried resistance-associated variants in 1 gene only, except for 1 genotype 1b patient carrying both Q80R in NS3 and Y93H in NS5A. All (100%) patients achieved sustained virologic response at follow-up Week 12 (SVR12). Conclusions: In the IMPACT study, NS3 or NS5A resistance-associated variants were detected by deep sequencing in 42% and 13% of patients, respectively. All patients achieved SVR12, regardless of the presence of baseline NS3 and/or NS5A resistance-associated variants.
RESISTANCE ANALYSIS IN 1284 PATIENTS WITH GENOTYPE 1 TO 6 HCV INFECTION TREATED WITH SOFOSBUVIR/VELPATASVIR IN THE PHASE 3 ASTRAL-1, ASTRAL-2, ASTRAL-3 AND ASTRAL-4 STUDIES

Company: Gilead  
Drug: Sofosbuvir  
Abstract Number: THU-216

Abstract Body: Background and Aims: The fixed dose combination of sofosbuvir/velpatasvir (SOF/VEL) was highly efficacious in GT 1-6 HCV infected patients in the ASTRAL studies. This analysis evaluated the impact of baseline resistance associated variants (RAVs) on treatment outcome and emergence of RAVs at relapse in HCV GT1-6 infected patients in the ASTRAL studies. Methods: NS5A and NS5B deep sequencing (1% cut off) was performed at baseline for all patients (n = 1028, ASTRAL-1 to 3; n = 256, ASTRAL-4) and at the time of relapse for patients with virologic failure. Results: The ASTRAL studies enrolled a diverse population of HCV with 35 known subtypes and 13 novel/mixed subtypes including 1 GT7 patient. Overall the prevalence of NS5A RAVs and NS5B RAVs was 36% and 7%, respectively. In patients with and without cirrhosis receiving SOF/VEL for 12 weeks in the ASTRAL-1-3 studies, high SVR12 rates were observed in patients with baseline NS5A RAVs (97–100% in GT1-2, 4–6 and 88% in GT3) (Table 1). Overall, the virologic failure rate was low (13/1028, 1.3%; 2 GT1; 10 GT3; 1 reinfection). The 2 GT1 infected patients who relapsed had NS5A Y93H or Y93N emerge. Within the GT3 patients with relapse, 6 had Y93H emerge and 4 maintained/enriched this baseline variant. SVR12 was achieved in all 77 patients who had baseline NS5B NI RAVs. No NS5B resistance was observed in patients with virologic failure. In ASTRAL-4, SVR12 rates were 100% (19/19) and 98% (46/47) in GT1 patients with or without baseline NS5A RAVs treated for 12 weeks with SOF/VEL+RBV and were lower in GT1 patients with baseline NS5A RAVs who received SOF/VEL for 12 (80%) or 24 (90%) weeks. Of note, resistance in Child Pugh B patients experiencing virologic failure with SOF/VEL ± RBV was similar to ASTRAL-1-3. Conclusions: SOF/VEL for 12 weeks resulted in high SVR in GT1-6 infected patients irrespective of baseline NS5A RAVs. NS5A resistance, but not SOF-resistance, was detected in patients with virologic failure. Similar results were observed in patients with Child Pugh B cirrhosis treated with SOF/VEL + RBV.

Table 1: SVR12 in Patients with or Without Baseline NS5A RAVs by HCV Genotype (SOF/VEL 12 Weeks; ASTRAL-1-3).

<table>
<thead>
<tr>
<th>Baseline NS5A RAVs</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOF</strong> in Patients</td>
<td>With</td>
<td>Without</td>
<td>With</td>
<td>Without</td>
<td>With</td>
<td>Without</td>
<td>With</td>
</tr>
<tr>
<td>NS5A RAVs, %</td>
<td>97.3%</td>
<td>100%</td>
<td>88.4%</td>
<td>100%</td>
<td>100%</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>(n/N)</td>
<td>(73/75)</td>
<td>(162/162)</td>
<td>(38/42)</td>
<td>(72/72)</td>
<td>(22/22)</td>
<td>(373/373)</td>
<td></td>
</tr>
<tr>
<td><strong>SOF</strong> in Patients</td>
<td>With</td>
<td>Without</td>
<td>With</td>
<td>Without</td>
<td>With</td>
<td>Without</td>
<td>With</td>
</tr>
<tr>
<td>NS5A RAVs, %</td>
<td>100%</td>
<td>100%</td>
<td>97.0%</td>
<td>100%</td>
<td>97.0%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>(n/N)</td>
<td>(70/70)</td>
<td>(225/225)</td>
<td>(48/48)</td>
<td>(28/28)</td>
<td>(863/863)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RESISTANCE ANALYSIS OF GENOTYPE 1 OR 3 HCV-INFECTED PATIENTS TREATED WITH SOFOSBUVIR/VELPATASVIR+GS-9857 FOR 6 OR 8 WEEKS

Company: Gilead
Drug: Sofosbuvir

Abstract Number: THU-220

Abstract Body: Background and Aims: Sofosbuvir (SOF), velpatasvir (VEL, GS-5816), and GS-9857 target three distinct HCV proteins, NS5B, NS5A, and NS3/4A, respectively. The LEPTON Phase 2 study, GS-US-337-1468, evaluated SOF/VEL + GS-9857 for 4, 6 or 8 weeks in different patient populations (EASL 2015 LP03; AASLD 2015 abstract 38). Here we describe the effect of baseline resistance associated variants (RAVs) on treatment outcome and treatment-emergent RAVs following SOF/VEL + GS-9857 treatment of GT1 patients with and without cirrhosis who had failed PEG/RBV ± protease inhibitor (PI), and GT3 patients with cirrhosis who were treatment naïve (TN) or had failed PEG/RBV. Methods: Treatment duration differed according to baseline characteristics: 8 weeks for GT1 patients who had failed prior PEG/RBV ± PI, and for TE GT3 patients; and 6 weeks for TN GT3 patients. NS3, NS5A and NS5B were amplified and deep sequenced (1% assay cut-off ) for all patients at baseline and those with virologic failure (all relapse). Results: Among the TN and PEG/RBV-experienced patients with cirrhosis, baseline NS3 and NS5A RAVs were detected in 29% (5/17) and 29% (5/17) in GT1 and in 14% (5/36) and 19% (7/36) in GT3, respectively (Table). All but one of these 22 patients with baseline RAVs achieved SVR (95%); this TN GT3 patient had the NS3 RAV Q168K (5.3%) at baseline which was not detected at relapse. In GT1 PI-experienced patients (all GT1a; median time from prior treatment 2 years), the baseline prevalence of NS3 and NS5A RAVs was 54% (15/28) and 29% (8/28), respectively. Among these patients, 83% (15/18) patients with baseline RAVs achieved SVR12. Treatment-emergent RAVs were detected in 1 of 5 patients who relapsed; this GT1a patient had NS3 RAVs at baseline and had emergent NS5AY93H at relapse (no other NS3 RAVS or any NS5A or NS5B RAVs emerged). A summary of the virology results from all of treatment arms of the LEPTON study will be presented. Conclusions: Baseline RAVs did not affect response to short durations of treatment with SOF/VEL + GS-9857 with the exception of PI experienced patients treated for 8 weeks. This 3-drug combination of direct acting antivirals has demonstrated a high barrier to resistance with rare emergence of RAVs in these short 6 and 8 week durations.
### Background and Aims

Despite recent advances in direct acting antiviral (DAA) therapy for hepatitis C virus (HCV), a variation in response remains between the different genotypes (G) with G3 being least responsive. Future HCV treatment is likely to include Sofosbuvir (SOF) and next wave NS5A inhibitors (such as Valpatasvir) but in patients with cirrhosis response rates are reduced and ribavirin (RBV) may still be required. Previous work from our laboratory, using a novel capture-fusion assay to study patient-derived HCV, suggests that pre-treatment RBV sensitivity influences pegylated interferon/ RBV response. Here we expand upon this observation by assessing RBV and SOF sensitivity in G3 patient-derived HCV.

### Results

10 patients were studied, all had advanced cirrhosis and were treated in the English Early Access Programme with sofosbuvir + ledipasvir (N = 5) or daclatasvir (N = 5). A reduced RBV and SOF sensitivity was observed in pre-treatment G3 isolates from patients who relapsed compared to patients with SVR (RBV IC50 = 0.48 ± 0.12 μM, SOF IC50 = 0.016 ± 0.0037 μM for SVR samples, RBV IC50 = 1.053 ± 0.16 μM, SOF IC50 0.18 ± 0.048 μM for relapse samples). Comparison of RBV and SOF sensitivity pre- and post- relapse from a G3 non-responder revealed a pre-treatment sensitivity to RBV and SOF (RBV IC50 = 0.43 μM, SOF IC50 = 0.028 μM), which was reduced post relapse (RBV IC50 > 1.25 μM, SOF IC50 > 0.25 μM). Analysis of viral sequencing data showed selection of NS5A RAVs Y93H and S62L in the post relapse sample compatible with reduced sensitivity to NS5A inhibitors. Additional mutations unique to the post-relapse sample were also observed in the Core, E1, E2, NS3, NS4, and NS5 regions but no signature sofosbuvir “resistance” motifs were seen.

### Conclusions

These data suggest that in patients with “hard to cure” HCV reduced sensitivity to sofosbuvir and ribavirin may be associated with treatment failure. Analysis of the viral sequencing data is underway to identify variants associated with these reductions in efficacy but early analysis suggests that no signature motif accounts for this modest reduction in viral sensitivity.
TREATMENT WITH SOFOSBUVIR + SIMEPREVIR FOR 12 WEEKS IN HCV COMPENSATED CIRRHOSIS (GENOTYPES 1 AND 4); THE USE OF RIBAVIRIN DOES NOT INFLUENCE SUSTAINED VIRAL RESPONSE

| Company | Gilead |
| Drug | Sofosbuvir |
| Abstract Number | SAT-103 |

**Abstract Body**

Background and Aims: The COSMOS study reported a high rate of sustained viral response (SVR) with Sofosbuvir + Simeprevir ± Ribavirin in patients with advanced liver fibrosis; however the number of cirrhotic patients included was small. Our aim was to assess the efficacy and safety of this therapeutic combination in patients with compensated cirrhosis. Methods: We analyze the outcome of our patients with HCV genotype 1 and 4 infection treated with Sofosbuvir + Simeprevir ± Ribavirin during the last year. The decision about use Ribavirin or not was a personal choice of the prescriber. The presence of Q80K polymorphism in HCV-genotype 1a infection was not explored in our patients. Cirrhosis (Stage 4 fibrosis) was defined by a transient elastography result ≥14 Kpascal. Results: A total of 79 patients were treated (45 Men/34 Women; mean age: 58.9 ± 9.9 years). Sixty-nine patients (87.3%) had cirrhosis. Baseline characteristics were: Child-Pugh A 89.9%; MELD 7.72 ± 1.9; Presence of esophageal varices 40.5%; History of hepatic decompensation 13.9%; and previous hepatocellular carcinoma 10%. Patients had infection by HCV-genotype 1b/1a/4: 67.1%/21.5%/8.9% and they were Naïve 32.9%, Relapsers 13.9%, Partial responders 8.9%, and Null responders 39.2%. Among cirrhotic patients Ribavirin was added to Sofosbuvir + Simeprevir in 49.2% and SVR was similar with and without Ribavirin (93.5% vs 88.8%, p = 0.65). In patients with cirrhosis SVR-4 was 93.7% and SVR-12 was 91.4%. No significant differences in SVR-12 were observed between patients treated with or without Ribavirin according to HCV-genotype or previous treatment response. SVR- 12 with and without RBV in genotype 1a (n = 12/2) was 100% vs 100%, in genotype 1b (n = 13/25) was 84.6% vs 88%; All patients with genotype 4 (n = 5) were treated with Ribavirin and reached SVR-12 (100%). SVR-12 with or without Ribavirin was 91.6% vs 83.3% in naïves (n = 12/6), 100% vs 100% in relapsers and partial responders (n = 6/5), and 90.9% vs 85.7% in null responders (n = 11/14). Three patients (3.8%) suffered severe adverse events, including one death and one discontinuation of therapy. Patients treated with Ribavirin presented a higher number of mild adverse events. Conclusions: 1) Treatment of compensated cirrhosis with Sofosbuvir + Simeprevir with or without Ribavirin reached a SVR- 12 of 91.4%. 2) Cirrhotic patients treated without Ribavirin achieved similar SVR-12 than those treated with Ribavirin.
SOFOSBUVIR PLUS VELPATASVIR FOR CHRONIC HCV GENOTYPE 1, 2, 3, AND 4 INFECTION

Company  Gilead
Drug       Sofosbuvir
Abstract Number  SAT-104

Abstract Body  Background and Aims: Hepatitis C virus (HCV) has infected approximately 170 million people worldwide. Sofosbuvir is a direct acting antiviral that inhibits HCV NS5B protein and has been approved to treat HCV in combination with other agents. Velpatasvir is another DAA that inhibits HCV NS5A protein. Recently, multiple studies have evaluated the efficacy of the combination (Sofosbuvir plus Velpatasvir) for the treatment of different HCV genotypes. Therefore, we performed this systematic review and meta-analysis to precisely estimate the sustained virologic response (SVR) achieved by Sofosbuvir plus Velpatasvir for chronic HCV genotype 1, 2, 3, and 4 Infection. Methods: We followed PRISMA statement guidelines during the preparation of this systematic review and meta-analysis. A computer literature search of PubMed, SCOPUS, web of knowledge, and Cochrane CENTRAL has been conducted using relevant keywords. Studies were screened for eligibility and data were extracted to an online data extraction form. SVR was pooled in a fixed effect model meta-analysis using Mantel–Haenszel method. Heterogeneity was assessed by visual inspection of the forest plots and measured by Chi-square and I-square tests. Statistical analysis was performed by OpenMeta[Analyst] software (by Center of Evidence Based Medicine http://www.cebm.brown.edu/open_meta/). Results: Five randomized controlled trials (n = 2,407 patients) were pooled in the final analysis. For non-cirrhotic patients who received 400 mg Sofosbuvir plus 100 mg Velpatasvir, SVR was 97.1% with 95% CI [92.7% to 101.5%]. For cirrhotic patients who received 400 mg Sofosbuvir plus 100 mg Velpatasvir, SVR were as follows (for genotype 1a, SVR = 97.8% with 95% CI [96.1% to 99.4%]; for genotype 1b, SVR = 99% with 95% CI [97.4% to 100%]; for genotype 2, SVR = 99.4% with 95% CI [98.4% to 100%]; for genotype 3, SVR = 64% with 95% CI [85.8% to 69.1%]; and for genotype 4, SVR = 99.7% with 95% CI [98.9% to 100%]). When Ribavirin was added to the treatment regimen, patients with genotype 1a showed less SVR (95.3% vs. 97.8%) while patients with genotype 3 achieved better SVR than without Ribavirin (94.7% vs. 64%). Conclusions: The treatment regimen of 400 mg Sofosbuvir plus 100 mg Velpatasvir was effective (SVR > 95%) for genotype 1, 2, and 4 HCV infection. But for genotype 3, Sofosbuvir plus Velpatasvir showed moderate SVR which improved with adding Ribavirin (64% vs. 94.7%)
THE COMBINATION OF DACLATASVIR AND SOFOSBUVIR FOR CURING GENOTYPE 2 PATIENTS WHO CANNOT TOLERATE RIBAVIRIN

Background and Aims: The current standard-of-care for treatment of HCV genotype 2 (GT-2) patients is the combination of sofosbuvir (SOF) with weight-based ribavirin (RBV). Patients with HCV GT-2 infection and ribavirin contraindications require the use of SOF plus NS5A inhibitor daclatasvir (DCV) which is not reimbursed everywhere. Methods: We conducted an open-label observational, prospective study on a subgroup of GT-2 patients either naïve or treatment experienced (TE) with contraindications to the use of RBV. Patients with cirrhosis of Child-Pugh-Turcotte (CPT) class A and B, or advanced fibrosis with co-morbidities were included. They were assigned to receive 12 or 24 weeks of SOF/DCV. The primary end point of the study was sustained virological response (SVR) defined as HCV RNA levels <12 IU/mL, 12 weeks post treatment. Results: Out of 106 patients with GT-2 who received treatment at our Unit from July 2014 to June 2015, 20 (18.8%) whose treatment could not be deferred, were ribavirin intolerant; 19 received SOF/DCV combination for 12 or 24 weeks. There were 10 males, 58% had cirrhosis, 58% were TE. All treated patients achieved SVR regardless of treatment duration. The most common adverse events (AEs) were fatigue, headache and nausea. No discontinuations due to AEs were observed. Two patients had oesophageal bleeding but continued treatment and achieved SVR; one patient developed HCC 12 weeks post-treatment, but remained HCV RNA undetectable. Conclusions: This study supports the use of SOF/DCV for 12 in non cirrhotics, or 24 weeks in cirrhotic GT-2 patients who cannot tolerate RBV, including those with decompensated disease.
SIGNIFICANT REDUCTIONS IN COSTS OF GENERIC PRODUCTION OF SOFOSBUVIR AND DACLATASVIR FOR HEPATITIS C TREATMENT IN LOW- AND MIDDLE-INCOME COUNTRIES

Company  Gilead
Drug  Sofosbuvir
Abstract Number  SAT-114

Abstract Body  Background and Aims: The current prices of sofosbuvir are US $50,000–84,000 in high-income countries. For 101 countries covered in generic sublicenses from the proprietor Gilead, the minimum current market price for sofosbuvir is US$480–940 for 12 weeks. Methods: The prices of Indian sofosbuvir and daclatasvir API exports were extracted from www.infodriveindia.com. Using per-kilogram API export prices and an algorithm used in previous price-estimation studies, we calculated target prices for generic sofosbuvir and daclatasvir. To per-pill API cost, we added a 40% markup for formulation, $0.35 per month for packaging, and a 50% profit margin. The calculation assumed market competition and optimization of production processes. Results: Between January 1 and November 11, 2015, over 5.2 tons of sofosbuvir were exported – enough to treat more than 150,000 patients – with prices decreasing by US$712/kg/month, and observed prices of US$2501/kg in early September (Figure). Over the same period, 113 kg of daclatasvir were exported – enough to treat more than 22,000 patients – with prices decreasing by US$1,417/kg/month to around $2,000/kg by the end of October (Figure). At current API prices, the cost-based generic price was calculated to be $178 for sofosbuvir and $23 for daclatasvir, per 12-week course. Conclusions: The costs of generic production of sofosbuvir and daclatasvir are rapidly decreasing. Sofosbuvir-daclatasvir combination treatment could be produced for US$201 per patient per 12-week course.
Background and Aims: Evidence-based treatment of the less common HCV genotypes 4–6 remains a challenge due to the scarcity of clinical data. The French ATU programme for daclatasvir (DCV) provided early access to DCV ahead of marketing authorisation to approximately 4,000 HCV infected patients across France with severe liver disease and no other treatment options. The efficacy of DCV plus sofosbuvir (SOF), with or without ribavirin (RBV), was assessed in patients with HCV genotype (GT) 4, GT 5 or GT 6 infection enrolled in the French ATU programme. Methods: Patients in the program received a recommended regimen of DCV (60 mg daily) plus SOF (400 mg daily) for 24 weeks. Addition of weight-based RBV and/or shorter treatment duration (12 weeks) was at physician discretion. The primary efficacy measure was sustained virological response at posttreatment week 12 (SVR12). Interim results are described. Results: Baseline data for all patients with GT 4–6, and SVR12 for GT 4, are discussed; SVR12 for GT 5 and GT 6 will be available for presentation. Overall 204 patients were assessed with GT 4 (n = 176), GT 5 (n = 22) or GT 6 (n = 6). Patients were predominantly male (71%), cirrhotic (76%) and peginterferon/RBV treatmentexperienced (82%); 35% were coinfected with HIV. Median baseline HCV RNA was similar across genotype groups (6.04–6.27 log10 IU/mL [overall range 1.08–7.48]), as was median screening platelet count (110–138 × 10⁹ cells/L [overall range 30–324]), and 27% of all patients had screening albumin <35 g/L. DCV + SOF was received by 82% of patients (12 weeks, 31%; 24 weeks, 51%) and DCV + SOF + RBV by 18% (12 weeks, 4%; 24 weeks, 14%). Overall SVR12 in GT 4 for DCV + SOF ± RBV (12 and 24 week treatment combined) was 90% (159/176): 90% (123/137) without RBV, and 97% (33/34) with RBV. For GT 4 patients with cirrhosis, overall SVR12 for DCV + SOF ± RBV was 90% (118/131): 88% (90/102) without RBV and 97% (28/29) with RBV. There were 2 treatment discontinuations for adverse events (AEs), 2 on-treatment deaths, and 1 discontinuation for AEs followed by death among the 176 GT 4 patients. Conclusions: In this, the largest real-world GT 4 cohort reported to date, the pangenotypic oral regimen of DCV plus SOF, with or without RBV, was effective and well tolerated in patients with both GT 4 infection and advanced liver disease. Assessment of genotypes 5 and 6 is ongoing.
Background and Aims: Ledipasvir/sofosbuvir (LDV/SOF) has yielded SVR12 rates of 96% in genotype 1, treatment-naïve HCV patients co-infected with HIV-1 in ION-4 (Naggie et al. NEJM 2015; 373 (8):705–13). Given the remarkable efficacy in clinical trials we aim to understand real-world outcomes across a heterogeneous co-infected population. The purpose of this study is to examine a real-world population to assess SVR12 rates in genotype 1 HCV patients co-infected with HIV-1 who were treated with LDV/SOF+/−RBV for 8, 12, or 24 weeks. Methods: Data were collected from providers and specialty pharmacies through Trio Health’s Innervation Platform, a cloud-based disease management program. All genotype 1 HCV patients co-infected with HIV-1 who initiated treatment with LDV/SOF+/−RBV, between Oct 2014 and Mar 2015 were included in the analysis (n = 140). Data collected includes 59% (82/140) treated in a community site, 69% (96/140) males, 29% (17/58) African Americans, 80% (17/138) genotype 1a, 46% (64/138) HCV treatment-experienced, 35% (49/139) with cirrhosis, 18% (11/62) with CRCL of L of <60 mL/min, 15% (13/87) with platelets <100 k/mL, and 22% (30/139) with a baseline viral RNA of 6 MMIU/mL or greater. 6% (8/140) patients were treated with 8 weeks, 74% (104/140) on 12 weeks, and 20% (28/140) on 24 weeks of LDV/SOF+/−RBV. Results: Overall SVR12 rate from this heterogeneous population was 98% (137/140). Of the 3 patients that did not achieve SVR12, 1 patient discontinued, 1 was lost to follow-up, and only 1 patient was a virological failure. SVR rates did not differ significantly among prior HCV treatment status (98% in treatment-experienced versus 97% in treatment-naïve), presence or absence of cirrhosis (98% in cirrhotic patients versus 99% in non-cirrhotics), creatinine clearance (100% in with CRCL <60 mL/min versus 82% with CRCL of 60+ mL/min), or duration of therapy (100%, 98%, 96% in 8, 12, 24 weeks of therapy respectively) Conclusions: Overall SVR in real world genotype 1 HCV patients coinfected with HIV-1 is 98% across regimens and various patient characteristics. SVR rates did not differ significantly among prior HCV treatment status, presence or absence of cirrhosis, creatinine clearance, or treatment duration.
SHORT DURATION TREATMENT WITH SOFOSBUVIR/VELPATASVIR PLUS GS-9857 IN TREATMENT-NAIVE GENOTYPE 1-6 HCV-INFECTED PATIENTS WITH OR WITHOUT CIRRHOSIS

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-138

Background and Aims: Sofosbuvir (SOF), velpatasvir (VEL), and GS-9857 target 3 distinct viral proteins: NS5B, NS5A, and NS3, respectively. All 3 of these DAAs are pangenotypic, with high barriers to resistance. The combination of these DAAs could reduce treatment duration across all patient populations, without reducing efficacy. Two Phase 2 studies, GS-US-367-1168 and GS-US-367-1169, evaluated whether short duration SOF/VEL (400 mg/100 mg) + GS-9857 (100 mg) can effectively treat genotype (GT) 1–6 HCV-infected, treatment-naive patients with or without cirrhosis. Methods: Patients were assigned SOF/VEL + GS-9857 administered orally once daily for 6 or 8 weeks based on the absence or presence of cirrhosis, respectively. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12) as assessed by the CAP/CTM HCV 2.0 assay (LLOQ = 15 IU/mL). NS5B, NS5A, and NS3 regions were amplified and deep sequenced (<1% cutoff) at baseline and at the time of virologic failure. Results: A total of 130 patients (52% GT1, 9% GT2, 30% GT3, 8% GT4, and 1% GT6) were treated: 58% male, 82% white, 68% with non-CC IL28B allele(s), and 48% had documented cirrhosis. SVR12 rates are shown in the Table. Baseline resistance-associated variants (RAVs) were detected in 55% of patients (22% NS5A; 22% NS3, 4% NS5B [no S282T], and 8% with resistance to multiple classes of DAA). All treatment failures (n = 18) were due to virologic relapse. Final NS5B, NS5A, and NS3 RAVs detected at the time of relapse will be presented. Frequent adverse events (AE, >10%) were headache, fatigue, diarrhea, and nausea; most were mild or moderate in severity. Two (2%) patients had treatment-emergent SAEs of atrial flutter (n = 1) and vertigo (n = 1); and both were considered not related to study drug by the investigator. Two (2%) patients discontinued therapy due to AE(s) of asthenia, diarrhea, vomiting, and dehydration (n = 1) at Week 7; and fatigue (n = 1) at Week 5; both achieved SVR12. No clinically significant laboratory abnormalities were observed. Conclusions: Treatment with SOF/VEL + GS-9857 administered once daily for 8 weeks is safe, well tolerated, and highly effective in treatment-naive, genotype 1–6 HCV-infected patients with cirrhosis. The 6 week treatment duration was associated with a higher relapse rate. This 3 drug combination is being further evaluated in Phase 3 trials, as a single tablet regimen for 8 weeks in treatment-naive patients, with or without cirrhosis.
SIMEPREVIR AND SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN IN GENOTYPE 1 CHRONIC HEPATITIS C PATIENTS: EFFICACY AND SAFETY IN REAL LIFE

Company: Gilead

Drug: Sofosbuvir

Abstract Number: SAT-152

Abstract Body: Background and Aims: Several direct-acting antiviral combinations are recommended for the treatment of genotype 1 (G1) chronic hepatitis C (CHC) patients. Simeprevir (SMV) and sofosbuvir (SOF) with or without ribavirin (RBV) has been shown to be highly efficient in some clinical trials. This study was conducted to assess the effectiveness and safety of this regimen in real-world patients with G1 CHC. Methods: A multicenter study was performed including 115 patients with G1 CHC who were undergoing a SMV-SOF combination for 12 weeks (with or without RBV at their doctor’s discretion). Variables analyzed: age, sex, BMI, genotype, subtype, basal fibrosis (transient elastography), presence of cirrhosis (>12.5 kPa and/or biopsy F4 and/or ultrasound diagnosis), analytical parameters, previous treatment experience, RBV use and the 12-week post-treatment sustained virological response (SVR12). Results: Baseline characteristics: 78 (68%) males, mean age of 57.6 ± 9.6 years, BMI of 25 (18–47) and G1 subtypes 1a and 1b were found in 26 (23%) and 83 (73%) of the patients, respectively. HCV-RNA was 1,080,000 UI/mL (11,390–17,000,000). The CC, CT and TT polymorphisms of the IL28 (n = 95 patients) were observed in 11%, 74% and 16% of the patients, respectively. The platelet count was 128,000/mm3 (13,200–347,000); the ALT value was 61 UI/mL (10–330); the assessment of fibrosis was 17.3 (4.4–75) kPa with cirrhosis in 93 (82%) patients. Treatment-experienced and treatment-naïve patients were 88 (77%) and 27 (23%), respectively. 60 of the treatment failures occurred with pegylated interferon and RBV and 28 with telaprevir or boceprevir associated. The global SVR12 rate was 91% (105/115 patients). The SVR was 90% without RBV and 92% with RBV (p = 0.7). The SVR12 observed in subgroups of patients treated with/without RBV was: cirrhotic patients, 91%/88% (p = 0.7); non-cirrhotic patients, 100%/100%; subtype 1a, 93%/100% (p = 1); subtype 1b, 91%/83% (p = 0.4); treatment-naïve, 90%/88% (p = 1); and treatmentexperienced, 93%/91% (p = 0.67). None of the cases required discontinuation of the treatment due to adverse events. Conclusions: High rates of SVR12, over 90% globally, were observed in this study of G1 CHC patients (more than 80% cirrhotic) undergoing a treatment with SMV and SOF. Non-significant differences in SVR12 rates were observed when RBV was added. Interruption of the treatment was not required due to the lack of side effects.
SOFOSBUVIR / LEDIPASVIR IN SPANISH PRISON POPULATION WITH CHRONIC HEPATITIS C

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-154

Background and Aims: Prison population is a high risk group for HBV, HCV and HIV. Prevalence of HCV infection in prisons is 10 times higher than in the general population: about 20% in 2014 vs. 1.6% in Spain. EASL recommend prioritize these patients regardless of fibrosis stage. Objectives: Preliminary evaluation of the treatment with Sofosbuvir/ Ledipasvir (SOF/LDV) in Spanish prison population. Methods: Prospective data collection of inmates infected with HCV patients treated in the Penitentiary Unit of Hospital Gregorio Marañón with SOF/LDV. Demographics (age, gender, route of infection) and clinical (state fibrosis, liver function, Child/MELD, HCV RNA) were included. Treatment consisted of SOF/LDV ± RBV for 12 or 24 weeks according to guidelines, giving priority to patients with F4. Results: A total of 49 inmates infected with HCV have started treatment with SOF/LDV, 26 (53.1%) 12 wk. and 23 (46.9%) 24 wk., including RBV 45 patients (91.8%). RBV dose ranged between 600 and 1,200 mg/day, with an average of 12.80 mg/kg/day (95% CI, 11.98 to 13.63). The median age is 47 years (range 21–60), 95.9% males (over 92% of the Spanish prison population are men); 87.8% of patients had a history of IDU and 85.7% of alcohol consumption. 53.1% had coinfection with HIV and HBV none. Only 2 patients had a BMI over 30. Regarding the state of fibrosis/cirrhosis: 35 (71.4%) were F4 (22 patients with a greater than 20 kPa FibroScan). Of cirrhotic 29 (82.9%) were Child-Pugh A and 6 (17.1%) were Child-Pugh B, 10 had a basal albumin less than 3.5 g/dL, 17 had less than 100,000 platelets/mm3 and 7 had a baseline MELD > 10. Genotype distribution was: 21 (42.9%) GT1 (15 GT1a, 2 GT1b, 4 without subtype), 21 (42.9%) GT3, 6 (12.2%) GT4 and 1 mixture GT1a and GT3a. On November 22, 2015: 17 patients had completed treatment, viral response rate observed at the end of treatment was 100%. SVR12 100% (2/2). From 35 patients with viral load results available in week 4: 30 undetectable, 3 detectable and only two quantifiable (32 and 79 IU respectively); in week 12: all 28 patients with undetectable viral load. No one patient discontinued treatment and only 6 reduced the initial dose of RBV. SVR12 data as well as safety and tolerability results will be updated at Congress. Conclusions: These results provide the first efficacy data with SOF/ LDV in Spanish prison population and show a response similar to that of general population.
TREATMENT OF HCV GENOTYPE 2 WITH SOFOSBUVIR AND RIBAVIRIN RESULTS IN LOW SVR RATES IN A REAL WORLD COHORT (GERMAN HEPATITIS C-REGISTRY, DHC-R)

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-155

Abstract Body
Background and Aims: Hepatitis C virus genotype 2 (HCV GT2) is generally considered to be easy to treat. Standard therapy is 12 weeks of sofosbuvir (SOF) and ribavirin (RBV). However, due to low patient numbers SVR rates varied substantially between studies. Alternative strategies with other regimen are not systematically studied for GT2. Methods: The DHC-R (Deutsches Hepatitis C-Register, German Hepatitis C-Registry) is a national multicenter real-world cohort including approx. 9,300 patients. Patients are treated at the discretion of the physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. This data analysis is based on 5,235 patients who were observed for at least 24 weeks after initiation of antiviral treatment. Results: 223 patients were infected with HCV GT2 and 194 had initiated treatment. Of the treated patients 135/223 (61%) were male, median age 54.5 years, 98% Caucasian origin, 139/194 (72%) were treatment naïve, 36/194 (19%) had liver cirrhosis, type 2 diabetes 17/194 (9%), opioid substitution (OST) 16/194 (8%), HCV-RNA >2 Mio IU/ mL 79/194 (41%) and >6 Mio IU/mL 26/194 (13%). Treatment regimens were as follows: SOF + RBV 12 weeks n = 146, SOF + RBV >12 weeks n = 10, PegIFN + RBV + SOF n = 5, DAC + SOF n = 5, LDV/SOF n = 1. At the time point of the analysis SVR 12 (ITT) was achieved with SOF + RBV 12 weeks in 89/119 (75%) patients and in 15/19 (79%) patients utilizing other treatments. The SVR rate for SOF + RBV 12 weeks in different subgroups is shown in Table 1. The SVR rate for SOF + RBV 12 weeks in patients treated per protocol excluding patients discontinuing therapy or being lost to follow up was 89/104 (85%). 5 patients (3%) discontinued therapy prematurely, of whom 1 patient had liver cirrhosis. Conclusions: In this large HCV GT2 cohort, therapy with SOF + RBV for 12 weeks achieved a low SVR rate compared to treatment outcomes expected from phase III trials. Even patients with favorable outcome factors did not achieve SVR rates above 80% in clinical practice. These findings highlight the need for establishing alternative treatment strategies for HCV GT2 patients.

Table 1: SVR ITT rates in subgroups of HCV GT2 patients treated with SOF+RBV for 12 weeks

<table>
<thead>
<tr>
<th>Characteristics Subgroup</th>
<th>SVR ITT, % (n/total) Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;70 years</td>
<td></td>
</tr>
<tr>
<td>Naïve</td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td></td>
</tr>
<tr>
<td>HCV-RNA &lt;6 Mio IU/ml</td>
<td></td>
</tr>
<tr>
<td>No OST</td>
<td></td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td></td>
</tr>
<tr>
<td>Pretreated</td>
<td></td>
</tr>
<tr>
<td>Cirrhotic</td>
<td></td>
</tr>
<tr>
<td>HCV-RNA &gt;6 Mio IU/ml</td>
<td></td>
</tr>
<tr>
<td>OST</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>76% (62/80)</td>
<td>50% (6/12)</td>
</tr>
<tr>
<td>79% (66/85)</td>
<td>53% (23/44)</td>
</tr>
<tr>
<td>78% (74/95)</td>
<td>53% (15/29)</td>
</tr>
<tr>
<td>76% (74/98)</td>
<td>78% (14/18)</td>
</tr>
<tr>
<td>74% (61/81)</td>
<td>83% (8/10)</td>
</tr>
</tbody>
</table>
Background and Aims: Optimal strategies for retreatment of patients with prior direct-acting antiviral (DAA) treatment failure are still not clear. We investigated the safety and efficacy of ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir (OBV/PTV/r) and dasabuvir (DSV) plus sofosbuvir (SOF) with or without ribavirin (RBV) in DAA-experienced patients with HCV genotype 1 (GT1) infection. Methods: Patients with GT1a infection were to receive OBV/PTV/r + DSV + SOF + RBV for 12 (without cirrhosis) or 24 weeks (with cirrhosis). Patients with GT1b infection received 12 weeks of OBV/PTV/r + DSV + SOF. All patients had a history of DAA treatment failure either due to on-treatment breakthrough or relapse. Presence of resistance-associated variants (RAVs) was assessed by deep sequencing. Efficacy was assessed by sustained virologic response at post-treatment week 12 (SVR12), defined as an HCV RNA <15 IU/mL. Safety and efficacy were assessed in all patients receiving at least 1 dose of study drugs. Results: Among 22 GT1 DAA-experienced patients enrolled, 20 had GT1a infection and 6 had compensated cirrhosis. Prior DAA experience included OBV/PTV/r + DSV (n = 14), OBV/PTV/r (n = 2), telaprevir + pegIFN/RBV (n = 2), SOF + pegIFN/RBV (n = 1), SOF + RBV (n = 1), simeprevir + samatasvir (n = 1), and simeprevir + SOF (n = 1). At baseline, 18/22 patients had RAVs in at least 1 of the 3 DAA targets, 6 of whom had RAVs in 2 targets, and 4 of whom had RAVs in all 3 targets. All but 1 patient had HCV RNA <15 IU/mL by treatment week 4. The non-cirrhotic GT1a patient with detectable viral load at week 4 extended treatment to 24 weeks. SVR12 was achieved in 14/15 (93%) patients treated for 12 weeks, and SVR4 was achieved in 7/7 patients receiving 24 weeks treatment. One GT1a patient with prior telaprevir + pegIFN/RBV experience and no baseline RAVs relapsed at post-treatment week 12. Two patients experienced serious adverse events (pneumonia and cellulitis), neither assessed as being related to study drugs. The patient with pneumonia discontinued study drug at week 10 but still achieved SVR12. Grade 3 laboratory abnormalities were rare. Conclusions: High SVR12 rates were achieved with the multitargeted regimen of OBV/PTV/r + DSV + SOF ± RBV in patients with DAA treatment experience, including those who previously failed the 3-DAA regimen and those with NS5A RAVs. Complete SVR12 data will be presented.
# SOFOSBUVIR PLUS SIMEPREVIR IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED EGYPTIAN PATIENTS WITH HEPATITIS C VIRUS INFECTION: A REAL LIFE EXPERIENCE

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>SAT-160</td>
</tr>
</tbody>
</table>

## Abstract Body

**Background and Aims:** Egypt has high prevalence of chronic HCV infection, more than 90% of patients are infected with genotype 4 and 22% of patients receiving ribavirin developed anaemia. This represents an urgent need for safe and highly effective therapies. We evaluated the efficacy and safety of one of interferon-free regimens; sofosbuvir (NS5B inhibitor) in combination with simeprevir (NS3/4A protease inhibitor) in Egyptian chronic HCV patients.

**Methods:** This is a prospective, observational study started June 2015 in four centres affiliated to the National Committee for the control of Viral Hepatitis in Egypt. Key inclusion criteria were age 18–70 years, evidence of chronic HCV infection for more than 6 months, positive HCV RNA by PCR, and absence of decompensated cirrhosis or other causes of liver disease. All patients (whether treatment naïve or treatment experienced; cirrhotics or not) received sofosbuvir (Sovaldi, Gilead Sciences) 400 mg plus simeprevir (OLYSIO, Janssen Therapeutics) 150 mg daily for 12 weeks without ribavirin. The primary end point was a sustained virologic response at 4 (SVR4; defined as HCV RNA < LLD at 4 weeks post-treatment) and 12 (SVR12; HCV RNA < LLD at 12 weeks post-treatment) weeks after the end of therapy.

**Results:** Out of 570 patients enrolled, 217 reached 4 weeks post treatment (SVR4) at the time of this abstract. Of those 217 patients: 174 (80.2%) were treatment-naïve and 43 (19.8%) treatment-experienced. 154 (71%) were male, 89 (41.01%) cirrhotic. End of treatment response was 99% (215/217) with only two patients were treatment failures (one naive cirrhotic and the other was treatment-experience non cirrhotic). To date, 207 out of 215 patients had HCV RNA < LLD (SVR4 = 96.3%). The other 8 patients who relapsed; 6 were cirrhotics (one of them was treatment experienced) and 2 were treatment experienced non cirrhotic. Overall sofosbuvir and simeprevir were well tolerated; most adverse events (AEs) were mild or moderate in severity. No Serious AEs. The most frequent AEs (>30% of patients) were consistent with the known side effects of sofosbuvir and simeprevir (fatigue, headache, pruritis and indirect hyperbilirubinemia). Skin rash was rare. By EASL time, more SVR4 and SVR12 data will be presented.

**Conclusions:** Sofosbuvir plus simeprevir without ribavirin for 12 weeks proved to be a simple, effective, and well-tolerated, interferon-free regimen in Egyptian patients with chronic HCV regardless of previous treatment or underlying cirrhosis.
SOFOSBUVIR-BASED, RIBAVIRIN-FREE REGIMENS IN PATIENTS WITH CHRONIC HEPATITIS C AND END-STAGE RENAL DISEASE: A LOOK AT SAFETY, TOLERABILITY AND EFFICACY

**Company**  
Gilead

**Drug**  
Sofosbuvir

**Abstract Number**  
SAT-164

**Abstract Body**  
Background and Aims: Sofosbuvir, a renally cleared, NS5B polymerase inhibitor, is one of the most appealing & versatile drugs available for the treatment of chronic hepatitis C (CHC) due to its efficacy, tolerability, pan-genotypic activity, low rate of resistance-associated variants, and minimal drug interactions. As a result, many of the currently approved regimens use sofosbuvir as backbone. Information on safety and efficacy of this particular drug in patients with end-stage renal disease (ESRD) on dialysis or with GFR < 30 mL/min is scant. We present interim data and the largest-to-date clinical experience on the tolerability, safety and efficacy of all-oral, ribavirin-free regimens containing daily, full-dose sofosbuvir in patients with ESRD. Methods: Data of CHC-infected patients with ESRD from three hepatology centers was collected. All patients included had CHC and ESRD on dialysis or GFR < 30 mL/min. All received an all-oral, ribavirin-free regimen containing sofosbuvir (sofosbuvir + simeprevir; sofosbuvir + ledipasvir or sofosbuvir + daclatasvir) for 12 or 24 weeks. Sofosbuvir was administered daily at full-dose (i.e. 400 mg). Results: Thirty-three patients with CHC and ESRD were included in the analysis. Most were on dialysis (n = 30, 90%). Nineteen (58%) were cirrhotic. Twenty (60%) were African American, 21 (64%) were genotype 1A, 11 were genotype 1B, and one was genotype 3. Twenty-six were treatment naïve. Twenty-seven (82%) have completed treatment; 6 are still on treatment (median duration 9 wks). Twenty-six were on sofosbuvir + simeprevir (19 on 12 wks; 7 on 24 wks); 6 were on sofosbuvir + ledipasvir, and one on sofosbuvir + daclatasvir. Eight (24%) have developed on-treatment adverse events (AE). Most AEs were classified as mild and included: insomnia (n = 4), headache (n = 3), nausea (n = 3), and fatigue (n = 2). One patient received a blood transfusion; another discontinued therapy after developing sepsis 5 weeks into treatment & going on hospice. The 24 patients who have reached 4-week follow up have undetectable viral load (100% SVR4), and all 21 patients who have reached 12-week follow up are cured (100%). Conclusions: Regimens that contain sofosbuvir, a renally cleared drug, seem to be well tolerated by CHC patients with ESRD, and the AEs resemble those of non-ESRD patients. The cure rates of ribavirin-free, sofosbuvir-based regimens also are remarkably higher than older regimens used in this special population, and comparable to other non-sofosbuvir-containing regimens recently studied.
REAL-LIFE RESULTS OF SOFOSBUVIR BASED THERAPY FOR EGYPTIAN PATIENTS WITH HEPATITIS C AND ADVANCED FIBROSIS-CIRRHOSIS

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-165

Abstract Body: Background and Aims: Egypt faces the largest burden of HCV infection in the world, and infection is predominantly with genotype 4. Triple therapy with sofosbuvir (SOF), pegylated interferon (PEG) and ribavirin (RBV) for 12 weeks, and dual therapy with SOF-RBV for 24 weeks have shown high sustained virological response (SVR) rates (97% and 90% respectively) in clinical trials that included HCV-genotype 4 patients, and their introduction in late 2014 in a national treatment program marked the beginning of a new era in HCV therapy in Egypt. The real-life results of this therapy for HCV genotype 4 is not known. Methods: Through a web-based registration system, the Egypt multicenter national treatment program started including compensated patients with advanced fibrosis or cirrhosis (F3-F4 by biopsy or fibroscan and FIB-4) in October 2014. Till November 2015, 175,000 patients have started treatment, and data are available at 12 weeks follow-up after end of therapy for 5,243 patients with advanced fibrosis-cirrhosis (F3-F4) (3,615 interferon eligible patients treated with SOF-PEG-RBV for 12 weeks (69%), and 1,628 interferon ineligible patients treated with SOF-RBV 24 weeks (31%)). Patients older than 60 years, and those with platelets <100,000, leucocyte count <3,000, neutrophils <1,500, or albumin <3 gm/dL were also selected for SOF-RBV treatment for 24 weeks. Response to therapy was assessed 12 weeks after end of treatment and SVR was considered if HCV-RNA was <15 IU/mL. Results: Patients in the SOF-RBV group were older, and more had cirrhosis and had lower platelets and albumin (a result of the selection criteria). By end of treatment, 163 (3.1%) patients failed to respond (3.2% with SOF-PEG-RBV, and 2.8% with SOF-RBV) and 5,080 patients had HCV-RNA below level of quantification (15 IU/mL) (96.9%). Subsequently, 543 patients (10.41%) relapsed (175 in the SOF-PEG-RBV group (4.5%) and 371 in the SOF-RBV group (27.1%). By 12 weeks after end of treatment, 4,534 (86.5%) patients had achieved SVR (3,572 (92.2%) in the SOF-PEG-RBV group and 962 (70.3%) in the SOF-RBV group). Conclusions: These real-life results from the largest national treatment program using SOF based therapy in patients with advanced fibrosis/cirrhosis showed a high SVR rate for 12 weeks of SOF-PEG-RBV and a lower SVR rate for 24 weeks of SOF-RBV, both being lower than results of clinical trials using same treatment regimens for HCV-genotype 4. More patients will reach SVR 12, and their results will be presented in the meeting.
Background and Aims: The once-daily fixed-dose combination tablet of sofosbuvir/velpatasvir (SOF/VEL) was evaluated for the treatment of genotype 1–6 HCV infection in three phase 3 studies in patients with and without compensated cirrhosis (ASTRAL-1, ASTRAL-2, ASTRAL-3). This analysis describes the safety of SOF/VEL across these 3 Phase 3 studies. Methods: Treatment-emergent adverse events (AEs) and laboratory abnormalities were assessed in patients randomized to SOF/VEL or placebo for 12 weeks in ASTRAL-1, SOF/VEL or SOF + RBV for 12 weeks in ASTRAL-2 and SOF/VEL for 12 weeks or SOF + RBV for 24 weeks in ASTRAL-3. Data was pooled by treatment regimen. Results: 1,558 patients were treated in the Phase 3 studies ASTRAL-1, ASTRAL-2, and ASTRAL-3: 1,035 with SOF/VEL, 116 with placebo, 132 with SOF + RBV for 12 weeks and 275 with SOF + RBV for 24 weeks. Twenty-two percent had compensated cirrhosis, 23% had a BMI ≥30 kg/m², 39% were female and 11% were ≥65 years old. In subjects who received SOF/VEL, headache, fatigue, nausea, and nasopharyngitis were the most common (incidence ≥10%) AEs reported with similar incidences in placebo–treated subjects. Table 1 provide a summary of adverse events by treatment regimen. Six deaths were reported, 3 patients treated with SOF/VEL and 3 patients treated with SOF + RBV for 24 weeks; none were assessed as related to study treatment. No SAEs occurred in placebo treated patients compared with 2.2% in SOF/VEL treated subjects. No SAE was assessed as related to SOF/VEL. Two subjects discontinued SOF/VEL for AEs; one patient discontinued after one day of treatment due to difficulty concentrating, headache, and anxiety and one patient discontinued after 13 days of treatment due to anxiety. Conclusions: Treatment with SOF/VEL for 12 weeks was well tolerated and had a safety profile similar to that of placebo treatment. Patients with and without compensated cirrhosis treated with SOF/VEL for 12 weeks may require minimal on treatment safety monitoring.
Background and Aims: HCV infection is highly prevalent among patients with a history of injecting drug use including those receiving opioid substitution therapy (OST). The Phase 3 ASTRAL studies demonstrated that treatment with the once-daily fixed-dose combination tablet of sofosbuvir/velpatasvir (SOF/VEL) was well tolerated and results in SVR12 rates >95% across all HCV genotypes. As neither SOF nor VEL have significant drug-drug interactions with medications commonly used for opioid substitution, these patients were not excluded from the SOF/VEL clinical program. Methods: This was a post-hoc analysis of data among patients treated with SOF/VEL in the Phase 3 ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies. Records of concomitant medications were reviewed for use of OST (including methadone, buprenorphine and buprenorphine/naloxone). Study drug adherence was self-reported. The safety and efficacy of SOF/VEL were compared between patients receiving, and not receiving OST. Results: Among 1,035 enrolled, 51 (5%) patients were receiving OST. Compared to those not receiving OST (n = 984), those receiving OST were more often male (77% vs. 60%) and had HCV genotype 3 infection (47% vs. 24%). Overall, the incidence of adverse events (AEs) was similar between those receiving and not receiving OST (one patient discontinued treatment for AEs in each group), although patients receiving OST had a higher incidence of Grade 3 and 4 AEs (14%) compared with non-OST patients (3%). SVR12 was similar (p = 0.26) in those receiving OST (96%, 49/51) and not receiving OST (98%, 966/984). The two patients who did not achieve SVR12 in the OST group included one who discontinued treatment after one dose of SOF/VEL due to AEs of anxiety, headache and disturbance in attention, and one who was discontinued after 5 days of treatment by the investigator for non-adherence to study medication. One patient not on OST and without a history of drug use and was determined to have HCV re-infection by deep sequencing of virus at time of virologic failure. Conclusions: The pangenotypic SOF/VEL FDC provides a well-tolerated and highly effective treatment for HCV infection for patients on opioid substitution therapy. Further prospective evaluation of SOF/VEL in people who inject drugs (PWIDs) is ongoing.
ON-TREATMENT ILLICIT DRUG USE DID NOT IMPACT TREATMENT OUTCOME DURING THERAPY WITH LEDIPASVIR-SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN IN THE PHASE 3 ION-1 STUDY

Company  Gilead

Drug  Sofosbuvir

Abstract Number  SAT-174

Abstract Body  Background and Aims: Positive drug testing has led to HCV treatment denial in some settings despite the lack of data demonstrating reduced safety or efficacy in these individuals. The impact of illicit drug use, including cannabinoids, on treatment outcome with IFN-free regimens has not been adequately assessed. This post-hoc analysis assessed the point prevalence of on-treatment illicit drug use and its impact on treatment outcome among patients treated with ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) in a Phase 3 clinical trial. Methods: Patients were excluded from ION-1 if they had clinically significant drug abuse as assessed by the investigator or a positive urine drug test at screening unexplained by a prescribed medication. Serum samples from treatment naïve HCV genotype 1 (GT 1)-infected patients enrolled in ION-1 collected at Weeks 8 and 12 of treatment with LDV/SOF ± RBV were retrospectively tested for drugs (amphetamines/methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, opiates, oxycodone, phencyclidine, propoxyphene and cannabinoids) by Enzyme-Linked Immunosorbent Assay (ELISA). SVR12 rates were compared between those with and without illicit drug use during therapy. Results: Of the 865 patients treated with LDV/SOF ± RBV in ION-1, 853 patients had Week 8 or Week 12 samples available for testing. The disposition and virologic outcome by on-treatment illicit drug use are provided in Table 1. Demographics were similar across the two groups. Overall, 30% (n = 259) tested positive for illicit drugs at either Week 8 or 12. Of 259 patients, 73% (188/259) had positive results at both time points. Fifty four percent (140/259) tested positive for cannabinoids only. The SVR and the overall virologic failure rates were comparable between these two groups (97% vs 100%; 0 vs <1%). Conclusions: Ongoing illicit drug use among treatment-naïve chronic HCV GT1 patients enrolled in clinical trials which excluded such patients was common, but did not impact the treatment outcome with LDV/SOF ± RBV, despite slightly higher rates of being lost to follow up.

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Yes (n = 259)</th>
<th>No (n = 594)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80% adherence, n(%)</td>
<td>233 (90)</td>
<td>545 (92)</td>
</tr>
<tr>
<td>Premature Discontinuation, n(%)</td>
<td>13 (5)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Adverse event, n(%)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrew consent, n(%)</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Lost to follow up, n(%)</td>
<td>9 (4)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Virologic Outcome

| SVR12, n(%)   | 251 (97) | 592 (>99) |
| Relapse, n(%) | 0          | 0          |
| On-treatment virologic failure, n(%) | 0          | 0          |
Background and Aims: Second generation direct-acting antiviral agents are integral to treatment for HCV infection but controversy exists regarding applicability of clinical trials to real-world effectiveness in community practice. Eight week courses of LDV/SOF have been supported in some studies, but data are limited on efficacy in real world use. We report virologic responses of patients with HCV genotype (GT) 1 infection receiving LDV/SOF with or without ribavirin (RBV) therapy for 8, 12 and 24 weeks. Methods: Approval was obtained from the Kaiser Permanente Institutional Review Board. Treatment naïve (TN) and treatment experienced (TE) HCV GT 1 patients who started LDV/SOF-based therapy were identified by electronic records and analyzed on an intent-to-treat basis. End-of-Treatment (EOT) and Sustained Viral Response 4 and 12 (SVR4, SVR12) were defined as HCV RNA less than the lower limit of quantification at completion of therapy, 4 and 12 weeks after completing therapy, respectively. Patients were deemed cirrhotic if either: (a) any history of biopsy-proven cirrhosis, (b) clinical manifestation(s) of cirrhosis or (c) AST to Platelet Ratio Index (APRI) >2.0 in the absence of biopsy ≤3 years prior to treatment; non-cirrhotic if either (a) no evidence of cirrhosis per biopsy ≤3 years prior or (b) APRI <0.5 in the absence of biopsy ≤3 years prior; or, otherwise undetermined fibrosis. Treatment was at clinician discretion, but 8 week courses were only recommended in TN, non-cirrhotic patients with HCV RNA <6,000,000 IU/mL. Results: 1,091 patients started LDV/SOF-based therapy; 383 started LDV/SOF/RBV therapy for 12 weeks and 708 started LDV/SOF therapy for up to 24 weeks. Respective baseline characteristics were median age (61, 60 years), male (69, 64%), TE (78, 14%), cirrhotic (24, 11%), non-cirrhotic (4, 13%) and undetermined fibrosis (72, 77%). We report EOT, SVR4 and SVR12 rates of 100%, 98% and 94% for patients receiving LDV/SOF/RBV therapy versus 100%, 98% and 93% for LDV/SOF therapy, respectively. Eight weeks of LDV/SOF therapy had comparable results to more aggressive regimens with 100%, 97% and 92% EOT, SVR4 and SVR12 respectively. [See Table] Conclusions: Eight week regimens were comparable in well-selected patients. For HCV GT 1 treated with LDV/SOF-based therapy, we found high EOT, SVR4 and SVR12 rates for patients of 92 to 100% which are very comparable to virologic responses reported in the published ION study series.
REAL-LIFE OUTCOMES OF 8 WEEKS REGIMEN OF SOFOSBUVIR AND LEDIPASVIR WITHOUT RIBAVIRIN, IN NON-CIRRHOTIC TREATMENT-NAÏVE HEPATITIS C GENOTYPE 1 PATIENTS WITH LESS THAN 6 MILLION IU/ML VIRAL LOAD

Company: Gilead

Drug: Sofosbuvir

Abstract Number: SAT-192

Abstract Body:

Background and Aims: 8 weeks fixed dose regimen of Sofosbuvir and Ledipasvir (Sof/Led) used in 150 mg/90 mg combination without ribavirin was noted to achieve high rates of sustained virologic response (SVR12) in clinical trials including patients Hepatitis C viral (HCV) genotype 1 infection. The effectiveness was noted to be robust in those without prior treatment, and with baseline HCV viral load of less than 6 million IU/mL. Generalizability of this regimen to general clinical practice, however, was advised with caution because of variable reliability of staging methods used, fluctuating nature of viral loads and lack of real-life confirmation.

Methods: We collected data of all patients who were provided 8 weeks Sof/Led by Burmans Specialty Pharmacy and were post 12 weeks of therapy completion. Burmans Specialty Pharmacy works with multiple prescribers and institutions, and serves a large population residing in PA, NJ, DE, and MD states in North Eastern region of United States. We gathered information of clinical outcomes from the pharmacy database and evaluated for any specific side effects in the patients treated at our institution.

Results: 192 patients included in the analysis were all treatment naïve HCV genotype 1 (1a: 68.2%, 1b: 25%, 1a/1b: 6.8%) patients with SVR12 data. Median (range) age was 59 (23–80) years, 50.5% were males while 62.5% were Caucasians, followed by 30.2% African Americans. Fibrosis stage was reported as F0 and F1 in 17.7% each, F2 in 26.6%, F3 in 17.2% and "non-cirrhotic" in 20.8%. Median (range) baseline HCV viral load was 1.3 million (493–5.6 million) IU/mL. SVR12 was achieved in 188 of 192 patients 97.9%. 4 patients relapsed after therapy completion, were African Americans (2 males, 2 females), 3 had F3 fibrosis and 1 was reported as "non-cirrhotic", 2 had genotype 1a, 1 had 1b, and 1 had 1a/1b. The SVR12 rates were low (90.9%) with F3, in particular in African American with F3 (12/15: 80%). There were no drug discontinuations and no severe adverse effects were reported. Overall the 8 weeks Sof/Led regimen was fairly well tolerated. Conclusions: 8 weeks therapy course of Sof/Led in HCV genotype 1 seems to be highly effective and is well-tolerated in real-life clinical practice. Use of this approach in African Americans with evidence of advanced fibrosis needs discretion, and further review of accumulating data.
LOW SUSTAINED VIROLOGIC RESPONSE (SVR) RATES IN GENOTYPE (GT) 2 AND 3 PATIENTS WITH QUANTIFIABLE HEPATITIS C VIRUS (HCV) AT WEEK 4 OF TREATMENT WITH SOFOSBUVIR (SOF) CONTAINING REGIMENS

Company: Gilead
Drug: Sofosbuvir
Abstract Number: SAT-193

Background and Aims: With the introduction of SOF in the United States, treatment guidelines eliminated response guided therapy (RGT) as on-treatment virologic response was not predictive of SVR in clinical trials. Members of our HCV ECHO (Extension for Community Healthcare Outcomes) collaborative (6 centers who treat HCV in specialty clinics and train primary care clinicians to treat HCV) follow shared treatment guidelines and continue to measure on treatment week 4 HCV RNA. Data presented in this abstract are from patients treated at a specialty clinic or by primary care clinicians. The purpose is to examine the association between week 4 HCV RNA and SVR in patients treated in real-world practice. Methods: This is a retrospective study of consecutive patients starting all oral, IFN-free treatment after January 2014 (genotype 2 or 3) or November 2014 (genotype 1). Variables examined included race, ethnicity, age, gender, baseline and 4 week HCV RNA, previous treatment, and AST to platelet ratio index (APRI). Results of univariate analysis were considered significant if p < 0.05. These variables were then incorporated into a multivariable model, significance set at p < 0.05. Results: A total of 522 patients were included: 288 patients with GT1 received ledipasvir/sofosbuvir with or without ribavirin (RBV) for 8 or 12 weeks and 234 patients with GT2 or 3 received SOF + RBV for 12, 16, or 24 weeks. Baseline demographics: mean age 56.8 years; 39% female; 72% White; 18% American Indian; 15% Hispanic; 42% APRI ≥ 1.0. Week 4 HCV RNA was detectable in 173 patients (33%), of which 67 were quantifiable. For GT1, GT2 and GT3, SVR was 95.1%, 91.1% and 76.7%, respectively. In multivariable analysis for GT1, no identifiable factors, including quantifiable week 4 HCV RNA, were associated with relapse. For GT2 and 3, multiple factors were independently associated with relapse including quantifiable week 4 HCV RNA (Odds Ratio (OR) 3.97, 95% Confidence Interval (CI) 1.40–11.26), APRI ≥ 1 (OR 10.1, 95% CI 3.32–30.8), and male gender (OR 4.77, 95% CI 1.7–13.72). Conclusions: In a real-world setting, a significant proportion of patients have detectable week 4 HCV RNA on treatment. A quantifiable week 4 HCV RNA is associated with relapse after SOF/RBV therapy in GT2 and 3 patients. More data are needed to formulate guidance for RGT for GT2 and GT3 patients. In contrast, GT1 patients had high SVR rates independent of week 4 on-treatment viral response.
Background and Aims: The once-daily fixed-dose combination tablet of sofosbuvir/velpatasvir (SOF/VEL) was evaluated for the treatment of genotype 1–6 HCV infection in three phase 3 studies in patients with and without compensated cirrhosis (ASTRAL-1, ASTRAL-2, ASTRAL-3). Overall SVR12 rates were >95% across all HCV genotypes. This post-hoc analysis assesses efficacy in patients with traditional negative predictors of response. Methods: This was a retrospective analysis of data from 1,035 patients treated with SOF/VEL in the Phase 3 ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies. Presence of cirrhosis was determined by histology, blood tests or transient elastography. Viral load and other clinical and laboratory assessments were determined prior to treatment with SOF/VEL. Prior treatment records were source verified and race was self-reported by the patient to the investigator. Results: Overall, 21% of patients had cirrhosis, 74% had HCV RNA ≥800,000 IU/mL, 28% had prior treatment failure, 12% were ≥65 years old and 6% were black. Table 1 provides SVR12 rates by HCV genotype overall and for each patient subgroup. The overall SVR12 rate was 98% and was ≥96% among all subgroups. In general SVR12 rates were lower in patients with genotype 3 HCV infection compared with other HCV genotypes but were ≥90% across all subgroups. Conclusions: The ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies enrolled a diverse patient population that included a significant number of patients with historically negative predictors of response. There was little effect of these factors on the efficacy of treatment with SOF/VEL for 12 weeks in subjects with genotype 1–6 HCV infection.
OUTCOME, SAFETY AND TOLERABILITY OF TREATING HEPATITIS C IN DECOMPENSATED CIRRHOTICS WITH LEDIPASVIR/SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN OR SOFOSBUVIR WITH RIBAVIRIN: REAL LIFE DATA. PRELIMINARY RESULTS OF RETROSPECTIVE SINGLE CENTER EXPERIENCE

Company: Gilead

Drug: Sofosbuvir

Abstract Number: SAT-196

Abstract Body: Background and Aims: Hepatitis C treatment in patients with decompensated cirrhosis has been a challenge due to poor tolerability and outcome. With the introduction of new direct-acting antivirals (DAAs), initial data are promising. Ledipasvir (LDV) Sofosbuvir (SOF) with or without Ribavirin (RBV) and SOF with RBV have shown good safety and tolerability profile in addition to excellent viral eradication with high sustained virological response (SVR12). Examine outcome, safety and tolerability of hepatitis C treatment using LDV/SOF with or without RBV and SOF with RBV in patients with decompensated cirrhosis at Loma Linda University Medical Center, Transplantation Institute, Loma Linda, California. Methods: After IRB approval, a retrospective chart review was conducted on 107 patients with decompensated cirrhosis secondary to hepatitis C infection. Patients were treated with several regimens of LDV/SOF with or without RBV or SOF with RBV from October 2013–May 2015. Results: 107 patients with Hepatitis C and decompensated cirrhosis were treated. 36 patients (34%) were listed for liver transplantation. Patient’s data, treatment regimens and outcome are listed in Figure. No treatment related serious adverse effects occurred. Treatment was discontinued in one patient at week 8 because of renal insufficiency, SVR 12 was achieved. Overall SVR12 was 82% in Genotype (GT) 1 & 4. Nine non responders: 8 relapsed, 1 breakthrough, 6 were treatment experienced, 8 were Child Pugh Class B. No specific treatment regimen was implicated in treatment failure. SVR12 was 60% in GT 2 & 3 (4/7 GT3, 2/3 GT2). Ribavirin dose reduction occurred in 40% of patients. No growth factors were needed. Conclusions: We report our single center experience of treating Hepatitis C GT 1 to 4 in patients with decompensated cirrhosis using LDV/SOF with or without RBV or SOF with RBV. Treatment was well tolerated with excellent SVR12 in GT 1 & 4. Despite small number, SVR12 in GT 2 & 3 was significantly lower. Larger prospective trials are needed to confirm these observations.
Background and Aims: Treatment of patients with recurrent Hepatitis C post liver transplantation has been a challenge due to poor tolerability and outcome. With the introduction of new direct-acting antivirals (DAAs), initial data are promising. Ledipasvir (LDV) and Sofosbuvir (SOF) have shown excellent viral eradication with high sustained virological response 12 weeks post treatment (SVR12) with good safety, tolerability and minimal drug-drug interactions with immunosuppressants. Our aim was to examine the outcome, safety and tolerability of treating recurrent Hepatitis C post liver transplantation using LDV/SOF with or without ribavirin (RBV) and SOF with RBV in patients with recurrent Hepatitis C post liver or liver/kidney transplantation at Loma Linda University Medical Center Transplantation Institute, Loma Linda, California. Methods: After IRB approval, a retrospective review of electronic medical records was conducted on 50 patients with recurrent hepatitis C infection post liver or liver/kidney transplantation who underwent treatment with LDV/SOF with or without RBV; or SOF with RBV from October 2013–May 2015. Results: Fifty patients with recurrent Hepatitis C post liver/liver/kidney transplantation were treated. Patient’s data and treatment regimens and outcomes are listed in the Figure. Thirty two patients completed week 12 after treatment. Overall SVR12 was 97%. All 24 patients with genotype 1 achieved SVR12 (100%). Seven of 8 patients with Genotype 2, 3 had SVR12 (82%). No treatment related serious side effects occurred. Treatment was discontinued in one patient because of rash at week 14, SVR 12 was achieved. Mycophenolate mofetil was discontinued in 1 patient due to neutropenia. Conclusions: Our single center experience of treating recurrent Hepatitis C genotypes 1, 2 and 3 after liver or liver/kidney transplantation with LDV/SOF with or without RBV or SOF with RBV was well tolerated with excellent SVR12. Ribavirin dose reduction was sufficient to manage related anemia without the use of growth factors. Mycophenolate mofetil was discontinued in 1 patient due to neutropenia. No adverse effects on graft function were recorded.
PHARMACOKINETIC ANALYSES OF LEDIPASVIR/SOFOSBUVIR IN HCV-INFECTED SUBJECTS WITH ADVANCED LIVER DISEASE AND/OR FOLLOWING LIVER TRANSPLANTATION

Company: Gilead

Drug: Sofosbuvir

Abstract Number: SAT-198

Abstract Body: Background and Aims: The fixed dose combination of ledipasvir/ sofosbuvir (LDV/SOF) + ribavirin (RBV) for 12 or 24 weeks in HCV-infected subjects with advanced liver disease and/or post-liver transplantation resulted in a high overall SVR12 rate of 92% (602/654). Pharmacokinetic (PK) data were collected to evaluate the impact of advanced liver disease and/or transplant on LDV/SOF exposures and exposure-response relationships. Methods: HCV-infected subjects with decompensated cirrhosis (Childs Pugh Turcotte category B or C) and/or who had received a liver transplant were enrolled in the Phase 2 studies (SOLAR-1 and -2) to receive LDV/SOF + RBV for 12 or 24 weeks. The PK of SOF, GS-331007 (predominant circulating metabolite of SOF), and LDV were evaluated in all subjects with measurable plasma concentrations using previously established population PK models. LDV/SOF PK in subjects with advanced liver disease and/or who underwent liver transplantation were compared to the historical LDV/SOF Phase 2/3 population. SOF, GS-331007, and LDV exposures were also evaluated by immunosuppressant regimens (ie, +/-cyclosporine) in posttransplant subjects and by treatment outcome. Results: Table 1 presents SOF, GS-331007, and LDV steady-state exposures across groups. LDV/SOF PK was similar across subjects with decompensated cirrhosis, regardless of liver transplantation. Relative to the historical LDV/SOF Phase 2/3 population, LDV and GS-331007 PK was not altered, but SOF exposure was approximately 2-fold higher across groups. The increase was not considered clinically important based on established exposure-safety analyses. Ledipasvir exposure was modestly (~45%) higher in subjects on a cyclosporine-containing regimen compared to those on noncyclosporine-containing regimens and remained within the range of exposures in LDV/SOF NDA population; there were no alterations in SOF or GS-331007 PK. Based on the available dataset, there were no clinically important differences in LDV/SOF PK between subjects who relapsed (N = 23) and subjects who achieved SVR12 (N = 601). Conclusions: There were no clinically relevant changes in LDV/ SOF PK exposure in subjects with advanced liver disease +/- transplantation, by immunosuppressant regimen, or treatment outcome. PK data, together with safety and efficacy data, support the use of LDV 90 mg/SOF 400 mg for 12 or 24 weeks for the treatment of HCV infection in subjects with advanced liver disease regardless of transplant status.
REAL WORLD EFFECTIVENESS OF LEDIPASVIR/SOFOSBUVIR (LDV/SOF) IN TREATMENT-EXPERIENCED CIRRHOTIC GENOTYPE 1 PATIENTS WITH CHRONIC HEPATITIS C: A COMPARATIVE ANALYSIS OF GILEAD SPONSORED TRIALS WITH 4 REAL-WORLD COHORTS

Company: Gilead
Drug: Sofosbuvir

Abstract Number: SAT-214

Background and Aims: Treatment-experienced (TE) cirrhotic HCV-infected patients are among the most difficult to treat. Diverse real-world LDV/SOF data is emerging & several single and multicenter cohorts have described treatment in this population. The current LDV/SOF EASL and AASLD/IDSA treatment recommendations for this population are based on several Phase 2/3 Gilead sponsored clinical trials (GST). SVR12 results in a large number of these TE cirrhotic patients from GST are described by Reddy et al., and range from 90 to 100% based on regimen. In addition, ION-4 and study 1118 (NCT01987453) describe LDV/SOF +/- RBV in a number of TE cirrhotic patients and are included in the analysis. Our aim is to describe and compare GST to 4 real world cohorts (RWC), including 1 large prospective, multicenter RWC from HCV-TRIO, two smaller multi-center RWC, and one single center RWC. Methods: In this comparative analysis, data from 9 Phase-2 and Phase-3 LDV/SOF studies in TE cirrhotic subjects is compared to several real-world, diverse populations. The RWC also include patients where data is lacking, such as simeprevir (SMV)/SOF failures. SVR12, safety, and baseline characteristics has been collated and compared. Results: SVR results in a large number of these TE cirrhotic patients are described by Reddy et al., ION-4 and study 1118 (9 total studies); SVR results for the combined studies are 110/118 (93%) with LDV/SOF for 12 weeks, 166/173 (96%) with LDV/SOF + RBV for 12 weeks, 98/100 (98%) with LDV/SOF for 24 weeks, and 22/22 (100%) with LDV/SOF + RBV for 24 weeks. In the RWC, HCV-TRIO, Pungpapong et al., Kohli et al., and Modi reported combined SVR of 110/131 (84%) with LDV/SOF for 12 weeks, 44/45 (96%) with LDV/SOF + RBV for 12 weeks, 331/ 359 (92%) with LDV/SOF for 24 weeks, 19/20 (95%) with LDV/SOF + RBV for 24 weeks. Conclusions: Real-world data in TE cirrhotics correlates closely with data seen in the GST. SVR rates were highest with LDV/SOF + RBV for 12 weeks and LDV/SOF ± RBV for 24 weeks. Discontinuations rates were low and the highest relapse rates were seen in those receiving LDV/SOF for 12 weeks. Likelihood of achieving SVR in the RWC was not affected by prior SMV and/or SOF exposure. This data supports current treatment recommendations.
THE EFFECT OF SOFOSBUVIR CONTAINING REGIMES IN PATIENTS WITH HCV GENOTYPE 3 INFECTION-A SCANDINAVIAN REAL-LIFE EXPERIENCE

Company  Gilead
Drug  Sofosbuvir
Abstract Number  SAT-228

Abstract Body  Background and Aims: In registration trials the effect of sofosbuvir (SOF) containing regimes have been modest among patients with genotype 3 infection especially in those with cirrhosis. We aimed at assessing the effect of SOF containing regimes in genotype 3 patients seen in our daily practices. Methods: We included 229 patients. The mean age was 55 years (range 31–77), 68% were men, 46% were treatment experienced and 67% of 220 with available staging were cirrhotic. Results: SVR4 was achieved in 213 (92%), 11 (5%) experienced virological relapse, 4 (2%) non-response and 1 (0.4%) viral breakthrough. Two patients died during treatment (unrelated to therapy). SVR4 was achieved in 140/154 cirrhotics (91%) compared to 63/66 (96%) of non-cirrhotics. Among those with a transient elastography available those with liver elasticity below 12.5 kPa, between 12.5 and 25 kPa, between 25 and 37.5 kPa and above 37.5 kPa the SVR4 rates were 100%, 93%, 96% and 75%, respectively (n = 144). Among all patients SVR 4 was obtained in 16/19 (84%) treated with SOF + RBV for 24 weeks, 53/55 (92%) of those treated with SOF + pegIFN + RBV for 12 weeks, 14/16 (88%) of those treated with Harvoni +/- RBV and 78/79 of those treated with SOF + DCV +/- RBV for 12 weeks and 44/49 (90%) of those treated SOF + DCV +/- RBV for 24 weeks. Conclusions: With SOF containing regimes for genotype 3 infected patients SVR 4 rates over 90% were achieved in a real world setting.

![Table showing SVR rates by regimen and cirrhosis status](image-url)
Background and Aims: The combination of Sofosbuvir/Daclatasvir/ Ribavirin (Sof/Dac/Rbv) for 12 weeks has shown good clinical efficacy amongst genotype 3 (GT3) patients with advanced fibrosis in a clinical trial setting, and within expanded access programmes (EAP). Outcomes from the use of this combination in routine clinical care are limited. We sought to examine the sustained viral response rates (SVR) of non EAP patients with GT3 infection and F3/4 disease, treated in Glasgow treatment centres. Methods: The Scottish Hepatitis C database was examined to identify GT3 patients with F3 (liver stiffness (LSM) ≥ 9.5 kPa 12.5 kPa, liver biopsy or imaging) treated in Glasgow treatment centres with Sof/Dac/Rbv for 12 weeks. Demographics, Child’s score, baseline viral load, week 4 and 12 PCR, SVR 4 and SVR12 were recorded, as were adverse events and premature discontinuations. HCV RNA was performed using Abbott Realtime PCR (lower limit of quantification (LLOQ) 12 IU/mL). Results: 27 patients met the inclusion criteria, 19 (70%) Male, mean age 49.3 (±7.4), 9 (33.3%) treatment experienced. 26/27 (96.3%) were cirrhotic of whom 15 (55.5%)/7 (25.9%)/4 (14.8%) were Child’s A/B/C respectively. 2 patients had HIV co infection, and one was post liver transplant. Median baseline viral load was 4.92 IU/mL (±1.1). At week 4 18 (69%) patients had RNA < 12 IU/mL (8 undetectable, 10 detectable), and 6 (31%) patients had quantifiable viraemia (median 22 IU/mL, range 14–40 IU/mL). Treatment was well tolerated with no discontinuations due to drug related adverse events. One patient’s treatment was stopped after 3 weeks due to an attempted hanging and subsequent psychiatric admission (excluded from SVR analysis), not judged related to treatment. One patient was admitted with variceal bleeding but maintained on treatment and achieved SVR. All patients achieved an end of treatment response (21 undetectable, 5 detectable <LLOQ). To date 16/19 (84.2%) of patients have achieved SVR12, including 4/5 (80%) of those with quantifiable RNA at week 4, and 4/5 (80%) of those detectable <LLOQ at end of treatment. Full SVR data for the cohort will be presented. Conclusions: Sof/Dac/Rib was safe and effective when used in routine clinical care, amongst a cohort with advanced liver disease. Neither quantifiable viraemia at week 4, nor detectable viraemia <LLOQ at end of treatment appear to impact on SVR12.
SOFOSBUVIR AND LEDIPASVIR VERSUS SOFOSBUVIR AND SIMEPREVIR COMBINATION THERAPY IN THE MANAGEMENT OF ACUTE HEPATITIS C: A RANDOMIZED OPEN LABEL PROSPECTIVE CLINICAL PILOT STUDY. SLAM C STUDY

Company  Gilead
Drug        Sofosbuvir
Abstract Number  SAT-234

Abstract Body
Background and Aims: Traditional management of acute HCV with peg IFN α2b and weight based RBV has had equivocal success with high SVR rates but significant adverse effects. Oral DAA’s have achieved SVR rates exceeding 95% in many cohorts and offer significant advantages particularly in vulnerable populations such as acute HCV. This clinical pilot study evaluates the efficacy of Sofosbuvir (SOF) with Ledipasvir (LDV) or Simeprevir (SIM) in acute Hepatitis C. Methods: 29 patients with a diagnosis of acute hepatitis C (negative past HCV antibody + new onset HCV RNA) were recruited from 6 inner city drug rehabilitation programs in Brooklyn, NY. They were divided into 2 groups; Group A (n = 14): SOF 400 mg + LDV 90 mg (daily once) – 4 weeks Group B (n = 15): SOF 400 mg + SIM 150 mg (daily once) – 8 weeks Labs: Prior to therapy HCV: RNA 0 and 12 weeks, sickle cell panel, LFT’s, CBC, Chem profile. On therapy HCV: RNA on day 0, 1 week, 4 week, 8 week followed by 16th week (SVR12 Group A) and 20th week (SVR12 Group B), LFT’s, CBC, Chem profile

Conclusions: This study demonstrates a high SVR with a very short course DAA’s in acute Hepatitis C. Both the groups achieved overall 93% without breakthrough or relapse. Overall the drugs were well tolerated with minimal side events. Larger trials will validate the efficacy and short treatment paradigm.
SOFOSBUVIR AND LEDIPASVIR IN ATTAINMENT OF SVR12 IN SICKLE CELL DISEASE (SCD) SUB-POPULATION WITH CHRONIC HEPATITIS C (CHC). A SINGLE CENTER PROSPECTIVE OPEN LABEL CLINICAL PILOT STUDY - SLASH C TRIAL

**Company**
Gilead

**Drug**
Sofosbuvir

**Abstract Number**
SAT-235

**Abstract Body**

Background and Aims: CHC is no longer a clinical challenge in the era of DAA’s. CHC and SCD contribute added challenges (sickle cell hepatopathy, accelerated fibrosis from chronic anemia and persistent secondary iron overload, ongoing cellular hypoxia induced by sheer stress). Severe anemia and sepsis with IFN induced bone marrow failure precluded therapy. This study evaluates the safety, efficacy and eradication of hepatitis C in this sub-group population with SCD. IL28B: TT allele in 21/24 patients, while CT allele in 3/24. All patients were placed LDV 90 mg + SOF 400 mg a day; with food for 12 weeks.

Methods: 24 patients were recruited from three sickle cell centers in NYC. Inclusion criteria: CHC (Geno specific with variation, diagnosed between 1998 and 2014) with SCD in remission (with sickle cell history >30 years). Conclusions: This study demonstrates that LDV and SOF combination in SCD patients with CHC is safe and well tolerated; with an SVR12 of 91.67% (22/24) with 8.3% (2/24) viral failure (in concomitant genotypes; 1a/4c and 1a/3c). The drugs were well tolerated with minimal side events. Larger trials will validate further.
Background and Aims: Patients with concomitant IBD and chronic HCV present a complex clinical challenge which is under studied thus no recommendations for HCV treatment exists. Prior IFN-based HCV treatment in this population was associated with both IBD exacerbations and increased toxicity. To evaluate the role and efficacy of new NS5A + NS5B inhibitors with and without RBV in treating CHC in moderate to severe IBD requiring biologic therapy. Methods: 35 patients were recruited from IBD centers in Brooklyn. Inclusion criteria CHC with IBD, Age: >18, HCV Viral Load: > 400,000 IU/mL, Genotype 1. Fibrotic Score: Metavir F1 to F4. Primary End Point: SVR12. Secondary End Point: IBD activity index, sustained remission with concomitant use of biologics (TNF alfa antagonists). Mayo score evaluation of mucosal healing. The patients were divided into two groups: Group A (n = 17)- RBV 1,000 mg + LDV and SOF; for 8 weeks and Group B (n = 18): LDV and SOF; for 12 weeks. All had base line RAV and end of treatment RAV’s and SVR 12. RAVs 5A polymorphism by Quest. Viral loads 0, 7, 14 days; 4th, 8th, 12th and 24th weeks. Conclusions: This study demonstrates the efficacy and safety of LDV and SOF for HCV genotype 1 (94.1 to 100% SVR 12) in patients with IBD in remission. Biological therapies (TNF alfa antagonists) were maintained for entire duration of HCV therapy with ongoing remission and complete mucosal healing. Both groups had SVR12 > 94%. 47% patients in Groups A had anemia secondary to hemolysis due to RBV. {Controlled with dose modification}. Overall, drugs were tolerated with manageable side events allowing 100% retention and completion of HCV therapy. Larger trials are needed to validate SVR rates and determine the potential role of ribavirin.
REAL-WORLD EFFECTIVENESS AND COST PER SUSTAINED VIRAL RESPONSE OF LEDIPASVIR/SOFOSBUVIR CHRONIC HEPATITIS C TREATMENT

Company: Gilead
Drug: Sofosbuvir

Abstract Number: SAT-240

Abstract Body: Background and Aims: Ledipasvir/Sofosbuvir (LDV/SOF) single tablet regimen (STR) is approved in Europe and the US for the treatment of chronic hepatitis C (CHC). With the emergence of novel, highly effective, and safe therapies and the expected demand for them, the need for optimal resource allocation is high. The cost per sustained viral response (SVR) is a measure which provides insights into the amount spent for achieving success in CHC therapy. This study aims to assess the safety, effectiveness, and the cost per SVR with LDV/SOF therapy in clinical practice in Germany. Methods: The first CHC patients treated with LDV/SOF in a single centre (with SVR after 12 weeks of follow-up (SVR12) available in April 2016) were included in the analysis. Baseline characteristics, prior treatment history, safety, effectiveness and cost per SVR were investigated using descriptive statistics.

Results: 219 patients met the inclusion criteria. 8w (50.2%), 12w (45.2%) or 24w (4.6%) treatment with LDV/SOF was initiated between 21/11/2014 and 01/06/2015. 21% of patients had ribavirin (R) added to the STR (79% of which F4). The mean (SD) age was 53 (11.4) years, 53% were male, 93% had at least one comorbidity. Genotype distribution: 53%, 35%, 7% and 5% for 1a, 1b, 3 and 4. METAVIR stage distribution: 38%, 17%, 13%, 10% and 22% for F0, F1, F2, F3 and F4. Median (IQR) HCV RNA at baseline was 1.02 (0.31–2.29) mil IU/mL. 5% (1%) of patients were HIV (HBV) co-infected. In patients with available outcome data, SVR4 was 98% (n = 188/191) and SVR12 was 97% (n = 200/207). Seven F4 patients did not achieve SVR12, two were naïve and five treatment experienced (TE). 7.3% (n = 16) had grade 3 or 4 adverse events (AE) and 5.9% (n = 13) were treatment-related. No AE lead to discontinuation. Median cost per SVR12 was €51,480; 73% of naïve patients and 66% of non-cirrhotic (NC) were on 8w duration; median cost per SVR was 81% lower in NC (€45,938) than in F4 patients and 61% lower in naïve (€46,273) versus TE. 1.0% of total costs were nontherapy. Full SVR12 and cost per SVR12 data will be available at the time of presentation.

Conclusions: This study suggests that as a result of a good tolerability profile, monitoring and AE related costs are minimal in LDV/SOF regimens. This study also suggests that, when the 8w regimen is used the cost per SVR is significantly lower in naïve and NC when compared to TE and cirrhotic patients, indicating an economic benefit of early treatment and the selection of highly effective and well tolerated therapies.
REAL-WORLD EFFECTIVENESS OF LEDIPASVIR/SOFOSBUVIR 8 WEEKS CHRONIC HEPATITIS C TREATMENT

Company  Gilead
Drug  Sofosbuvir

Abstract Number  SAT-243

Abstract Body  Background and Aims: Ledipasvir/Sofosbuvir (LDV/SOF) single tablet regimen (STR) is approved in Europe for the treatment of chronic hepatitis C (CHC) patients with genotypes (GT) 1, 3 and 4. The ION-3 study showed 8 weeks (8w) of LDV/SOF treatment was noninferior to 12 weeks in previously untreated GT1 patients without cirrhosis with no benefit for the addition of ribavirin. According to the SmPC 8w may be considered in this population. The aim of the present analysis is to characterise the population receiving 8w LDV/SOF and to describe outcomes in clinical practice in Germany. Methods: The first CHC patients treated with 8w LDV/SOF in a single centre (with SVR after 12 weeks of follow-up (SVR12) available in April 2016) were included in the analysis. Baseline characteristics, prior treatment history, safety and effectiveness were investigated using descriptive statistics. Results: 110 patients met the inclusion criteria for this analysis. Patients initiated 8w LDV/SOF treatment between 21/11/2014 and 01/06/2015. No patient had ribavirin added to the STR. The mean (SD) age was 49.8 (11.7) years; 42.7% were males. The genotype distribution was 49%, 49% and 2% for 1a, 1b and 4. No patient had cirrhosis. The METAVIR stage distribution of non-cirrhotic patients at baseline was 53.6%, 24.6%, 17.3% and 4.5% for F0, F1, F2 and F3. No patient had ribavirin added to the STR. The mean (SD) age was 49.8 (11.7) years; 42.7% were males. The genotype distribution was 49%, 49% and 2% for 1a, 1b and 4. No patient had cirrhosis. The METAVIR stage distribution of non-cirrhotic patients at baseline was 53.6%, 24.6%, 17.3% and 4.5% for F0, F1, F2 and F3. Median (range) HCV RNA at baseline was 8.89 (Q1–Q3 0.20–2.24; Min–Max 0.00–18.62) million IU/mL, 4 patients had HCV RNA ≥ 6 million IU/mL (7.1, 11.5, 13.8 and 18.6 million IU/mL; METAVIR stages F2, F0, F0 and F0). 3.6% (0%) of patients were HIV (HBV) coinfected. 97% of the patients were treatment-naïve. One patient had relapsed after IFN/RBV therapy and two patients had null response to IFN monotherapy. 93% of patients reported comorbidities; depression (16%) and arterial hypertension (10%) were common. To date, no discontinuations have been observed; 1.9% of patients experienced grade 3 or 4 adverse events, one was possibly related to LDV/SOF. 103 (94%) of patients achieved SVR12 and all were undetectable. 100% (103/103) of patients achieved SVR12. Full SVR12 information will be available at the conference. Conclusions: 8w LDV/SOF is predominantly prescribed according to the SPC for treatment-naïve non-cirrhotic CHC patients with HCV RNA <6 million IU/mL at baseline. The preliminary results of this real world study indicate that in line with clinical trials, an 8w regimen of LDV/SOF, is a highly effective and well tolerated if used in patients according to the EMA label.
SOFOSBUVIR/LEDIPASVIR WITHOUT RIBAVIRIN IN THE TREATMENT OF ASIANS WITH CHRONIC HEPATITIS C VIRUS GENOTYPE 6 IN THE UNITED STATES: COMMUNITY-BASED REAL WORLD OUTCOMES

Company: Gilead

Drug: Sofosbuvir

Abstract Number: SAT-254

Abstract Body: Background and Aims: Sofosbuvir/Ledipasvir (SOF/LDV) is the first reported safe and effective all-oral regimen for the treatment of chronic hepatitis C virus (HCV) genotype 6 infection. Phase 3 clinical trial data reported sustained virologic response 12 weeks after treatment end (SVR12) of 96% among a cohort of 25 patients. The current study aims to provide data on real world treatment outcomes in a large community-based gastroenterology practice in the United States. Methods: We retrospectively evaluated 62 adults (age ≥ 18) with chronic HCV GT6 treated with SOF/LDV without ribavirin at a large U. S. community gastroenterology clinic from November 2014 to November 2015. The majority (98.4%) were Vietnamese ethnicity. Rates of undetectable virus at week 4 on treatment, at end of treatment (EOT), and SVR12 were stratified by presence of cirrhosis and prior treatment experience (treatment naïve vs. treatment experienced). During the study period, 52 patients completed treatment, and 24 patients had SVR12 data. Results: Among the 62 patients with chronic HCV GT6 treated with SOF/LDV, 50.0% (n = 31) were male and the mean age at start of treatment was 66.1 years (SD 9.9). 40.3% (n = 25) had cirrhosis and 16.1% (n = 10) were treatment experienced with pegylated interferon and ribavirin. Overall, 97.0% (n = 32) had undetectable virus at on treatment week 4, 96.2% (n = 50) had undetectable virus at EOT, and 95.8% (n = 23) achieved SVR12 (Table). When stratified by presence of cirrhosis, undetectable virus at EOT was achieved in 96.8% (n = 30) of non-cirrhotics and 95.2% (n = 20) of cirrhotics. SVR12 was achieved in 100% (n = 15) of non-cirrhotics and 88.9% (n = 8) of cirrhotics. When stratified by treatment experience, undetectable virus at EOT was achieved in 97.7% (n = 42) of treatment naïve and 88.9% (n = 8) of treatment experienced patients. SVR12 was achieved in 95.2% (n = 20) of treatment naïve and 100% (n = 3) of treatment experienced patients. Adverse events reported included headache (n = 6), fatigue (n = 6), insomnia (n = 3), nausea (n = 1), rash (n = 1), and anemia (n = 1). No dose modification was needed and no patients discontinued therapy. Conclusions: Among a large community-based real world cohort of Asian chronic HCV GT6 patients in the United States, all oral SOF/LDV without ribavirin is a safe and effective treatment regimen that achieves high rates of SVR12. While up to 12.8% of patients reported mild adverse events, all patients completed the entire treatment course.
ON TREATMENT HCV RNA AS A PREDICTOR OF SVR12 IN PATIENTS WITH GENOTYPE 1-6 HCV INFECTION TREATED WITH SOFOSBUVIR/VELPATASVIR FIXED DOSE COMBINATION FOR 12 WEEKS: AN ANALYSIS OF THE ASTRAL-1, ASTRAL-2, AND ASTRAL-3 STUDIES

Company: Gilead

Drug: Sofosbuvir

Abstract Number: SAT-257

Abstract Body: Background and Aims: The once-daily fixed-dose combination tablet of sofosbuvir/velpatasvir resulted in high SVR12 rates in patients with genotype 1–6 HCV infection in the Phase 3 ASTRAL-1, ASTRAL-2 and ASTRAL-3 studies. The aim of this analysis was to explore whether early viral response was predictive of eventual treatment success. Methods: This was a retrospective analysis of data from 1,035 patients with genotype 1–6 HCV infection treated with SOF/VEL for 12 weeks in the Phase 3 ASTRAL 1, -2 and -3 studies. Patient plasma samples were analyzed using the COBAS Ampliprep/ COBAS Taqman v2.0 with LLOQ = 15 IU/mL. SVR12 rates for subjects with HCV RNA ≥ LLOQ, HCV RNA < LLOQ, and HCV RNA < LLOQ not detected at treatment week 1, 2 and 4 were calculated. Subject who did not achieve SVR12 due to non-virologic reasons (lost to follow-up, death, withdrew consent etc.) were excluded from the analyses. Results: 1,035 patients with genotype 1–6 HCV infection were treated with SOF/VEL for 12 weeks in the ASTRAL-1, 2, and 3 studies and 1,028 either achieved SVR12 or had virologic failure. Across all HCV genotypes, there were rapid and sustained declines in HCV RNA during treatment with SOF/VEL. HCV RNA < LLOQ at week 1, 2 and 4 were observed in 18%, 58% and 91% of patients, respectively. Table 1 presents the overall SVR12 rates, and SVR12 rates for patients with HCV RNA < LLOQ, HCV RNA < LLOQ not detected, and HCV RNA > LLOQ at Week 2 of treatment. Similar results were observed at week 1 and week 4 of treatment. Conclusions: Assessment of HCV RNA at early timepoints (weeks 1, 2 or 4) in patients with genotype 1–6 HCV infection during treatment with SOF/VEL has limited clinical utility for determining treatment outcome, or futility.
PHARMACOKINETIC INTERACTIONS BETWEEN SIMEPREVIR AND LEDIPASVIR IN TREATMENT-NAÏVE HEPATITIS C VIRUS GENOTYPE 1-INFECTED PATIENTS WITHOUT CIRRHOSIS TREATED WITH A SIMEPREVIR/SOFOSBUVIR/LEDIPASVIR REGIMEN

Company: Gilead
Drug: Sofosbuvir

Abstract Number: SAT-264

Abstract Body: Background and Aims: The drug interaction between simeprevir (NS3/4A protease inhibitor) and ledipasvir (NS5A replication complex inhibitor) was investigated in treatment-naïve hepatitis C virus genotype 1-infected patients without cirrhosis, treated with simeprevir/sofosbuvir/ledipasvir in a Phase 2, open-label study (NCT02421211). Methods: Patients (N = 40) were randomised to 1 of 2 panels (n = 20 in each). Panel 1: patients received simeprevir 150mg and sofosbuvir 400mg once daily from Day 1–Day 14. From Day 15–Day 70, patients received simeprevir 150mg and ledipasvir/sofosbuvir 90/400 mg once daily. Panel 2: patients received ledipasvir/sofosbuvir 90/400mg once daily from Day 1–Day 14. From Day 15 – Day 56, patients received simeprevir 150 mg and ledipasvir/sofosbuvir 90/400 mg once daily. Total treatment duration in Panel 1 and Panel 2 was 10 weeks and 8 weeks, of which 8 and 6 weeks, respectively, were with simeprevir + ledipasvir/sofosbuvir. The plasma concentration versus time profiles of simeprevir in the presence or absence of ledipasvir (Panel 1: Day 28 versus Day 14) and of ledipasvir in the presence or absence of simeprevir (Panel 2: Day 28 versus Day 14) were assessed. Safety data up to Day 28 are reported. Results: Baseline characteristics: male, 45%; genotype 1a/1b, 20/80%; NS3/NS5A resistance-associated variants, 8/20%; no NS5B S282T was observed at baseline. The maximum plasma concentration and area under the plasma concentration-time curve during the dosing interval were, respectively, 2.45- and 3.13-fold higher, for simeprevir with versus without ledipasvir (Panel 1); 1.60- and 1.70-fold higher, for ledipasvir with versus without simeprevir (Panel 2), based on least squares means ratios. Adverse events (AEs) occurred in 73% (29/40) of patients; all Grade 1/2 and the most common was photosensitivity (33%). No serious AEs or treatment discontinuations due to AEs were reported. Grade 3 treatment-emergent laboratory abnormalities were observed in Panel 1 (n = 2; pancreatic amylase elevation and hyperbilirubinaemia). Sustained virologic response 12 weeks after the end of treatment will be presented. Conclusions: The combination of simeprevir and ledipasvir, in the presence of sofosbuvir, led to no clinically significant increase in ledipasvir and a moderate increase in simeprevir plasma concentrations, respectively. The safety profile was similar to that of the single drugs; however, photosensitivity was reported more frequently. Funding: Janssen.
Background and Aims: The once-daily fixed-dose combination (FDC) tablet of sofosbuvir/velpatasvir (SOF/VEL) has demonstrated high efficacy in genotypes 1–6 HCV-infected patients when administered for 12 weeks. This analysis describes the safety and efficacy of SOF/VEL FDC in patients previously treated with SOF/VEL placebo in the phase 3 registrational, ASTRAL-1 study.

Methods: HCV infected patients who received placebo treatment in the ASTRAL-1 study were enrolled in this single arm, open label deferred treatment study following the completion of visits in the original trial. All patients received SOF/VEL (400 mg/100 mg once daily) for 12 weeks. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12). Secondary endpoints included safety, resistance and additional efficacy outcomes.

Results: A total of 111 patients were enrolled and treated with SOF/VEL for 12 weeks. Overall 59% were male, 77% were white, 32% had IL28B CC genotype, 28% were treatment experienced and 17% had compensated cirrhosis. The HCV genotype distribution was 39% GT1a, 17% GT1b, 18% GT2, 17% GT4 and 8% GT6. HCV RNA declined rapidly with 95% of patients achieving HCV RNA < LLOQ (<15 IU/L) at treatment week 4. In this interim analysis, 17 of 18 patients were <LLOQ at the post treatment week 12 visit. No patient discontinued study treatment due to adverse events. The most common AEs (>10%) in patients were headache, fatigue and nausea occurring at similar rates observed during placebo treatment (Table 1). Five patients experienced serious adverse events; all were considered unrelated to study drugs (cellulitis, hepatocellular carcinoma, fracture, cholestasis and meniscus tear). No significant laboratory abnormalities were observed. Efficacy and safety outcomes including final SVR12 and the impact of HCV resistance variants on outcome will be presented. Conclusions: The IFN-free, RBV-free, single tablet regimen of SOF/VEL administered once daily for 12 weeks was well tolerated in genotype 1, 2, 4 and 6 HCV infected patients regardless of past treatment experience or presence of cirrhosis.

Table 1: Adverse events occurring during treatment (>10% of patients)

<table>
<thead>
<tr>
<th></th>
<th>AEs occurring during placebo treatment</th>
<th>AEs occurring on SOF/VEL treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 110</td>
<td>N = 110</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (28%)</td>
<td>23 (21%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (22%)</td>
<td>17 (16%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (11%)</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 (11%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (10%)</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>
Background and Aims: The combination of Sofosbuvir (SOF), a polymerase inhibitor, plus Simeprevir (SMV), a protease inhibitor (PI), with or without ribavirin (RBV), has shown a good efficacy and safety profile in compensated cirrhotic patients infected with the hepatitis C virus (HCV) genotype (GT) 1 or 4. To date, there is no available data regarding the efficacy of this combination in real-life cirrhotic patients in Spain. The aim of this multicentric study was to assess the Spanish clinical experience using SOF/SMV (±RBV) in a large cohort of real-life compensated cirrhotic patients. Methods: Retrospective analysis of data from GT1 and GT4 infected cirrhotic patients treated with this oral antiviral combination. Results: Six-hundred and 22 cirrhotic patients were included. Cirrhosis was defined according to clinical, histological, ultrasonographic or elastographic criteria. The majority of patients were male (62%) and the median age was 59 years (23–80). Patients were infected with GT1a (20%), 1b (67%) or 4 (10%). The median transient elastographic measurement was 21.8 KPa (P25 16.6; P75 33.3); the MELD score was 8(5–26) and the majority of patients (73.5%) were Child-Pugh A at baseline. Up to 58.5% of patients had previously failed to antiviral therapies; importantly 17% of them had already received a PI-based regimen. Baseline median ALT was 69(5– 513) and viral load (HCV-RNA) was 6.06 log10 IU/mL (1.28–8.29). The majority of patients (78%) were treated for 12 weeks and 62% of the cohort received RBV. Fourteen patients are still on treatment; 8 patients had to prematurely discontinue therapy (1 due to an allergic reaction, 1 committed suicide, 1 had hepatocellular carcinoma progression, 2 patients presented liver decompensation and in 3 cases was unknown). At the end of treatment (EOT), all patients had undetectable serum HCV-RNA. The rates of sustained virological response (SVR) 4 and 12 weeks after therapy were 95.5% (485/505) and 88.5% (415/469), respectively. SVR rate was similar among patients, regardless of the use or not of RBV. There were 54 (8.7%) reported virological failures. Safety profile will be reported. Conclusions: The combination of SOF/SMV (with or without RBV) is very effective in cirrhotic patients infected with GT1 and 4 in Spain. The high prevalence of G1b infection may explain the higher efficacy compared with other real-life cohorts.
ANTIVIRAL TREATMENT IN PATIENTS WITH ADVANCED HCV CIRRHOSIS USING SOFOSBUVIR AND LEDIPASVIR/ DACLATASVIR WITH OR WITHOUT RIBAVIRIN – 6 AND 12 MONTH OUTCOMES COMPARED TO UNTREATED PATIENTS

Company: Gilead

Drug: Sofosbuvir

Abstract Number: PS097

Abstract Body: Background and Aims: Direct acting antivirals (DAAs) successfully clear hepatitis C (HCV) infection without the use of interferon, allowing treatment of patients with advanced liver disease. Since April 2014 the English Expanded Access Program (EAP) has provided DAAs for patients with advanced HCV cirrhosis, using sofosbuvir (SOF) combined with ledipasvir (LDV) or daclatasvir (DCV). Aim: to study the virological and functional outcomes up to 12 months after end of DAA therapy in advanced HCV cirrhosis, in comparison to untreated patients. Methods: We included patients fulfilling NHS England EAP criteria, who received 12 weeks of SOF and LDV or DCV, with or without ribavirin. Patients consented to prospective data collection by HCV Research UK (HCVRUK). Two groups of patients with untreated HCV advanced cirrhosis were selected retrospectively from HCVRUK for functional outcome comparison (a) patients with decompensated cirrhosis enrolled at least 6 months prior to the initiation of the EAP, who did NOT subsequently enter EAP; (b) EAP patients for whom retrospective data were available for the period 6 months prior to EAP therapy. Outcome measures: HCV undetectable 12 weeks after treatment end (SVR12), change in MELD score and serious adverse events within 12 months. Results: We report on 467 treated patients, consisting mainly genotypes 1 (G1) and 3 (G3) HCV infections. Patients had advanced liver disease – 88% with past or current decompensation, median MELD score was 11. SVR12 was significantly higher for G1 than G3 (90 vs. 69%, p < 0.0001), and in ribavirin-containing regimens. High body mass index and detectable virus at treatment week 2 were associated with lower SVR. Compared to untreated patients (n = 261) over a 6 month period, treated patients had more frequent MELD score improvements, and fewer decompensation events (18 vs. 28%, p = 0.0006). All-cause adverse outcomes (MELD increase ≥2 and any serious adverse event) were reduced (52% vs. 64%, p = 0.004) but there was no significant difference in incidence of primary liver cancer (6 vs. 8%), sepsis (7 vs. 6%), liver transplantation (4 vs. 6%) or death (6 vs. 3%). Conclusions: High SVR rates were achieved with 12 weeks of DAAs in this large real-life patient cohort with advanced cirrhosis, who previously had limited treatment options. HCV treatment was associated with early improvements in liver function. This is clinically relevant in a population with poor prognosis. The longer term outcome of the treated patients over 12 months follow-up will be reported.
RESISTANCE ANALYSES FOR LEDIPASVIR/SOFOSBUVIR CONTAINING REGIMENS IN PATIENTS INFECTED WITH CHRONIC HCV WHO HAVE ADVANCED LIVER DISEASE OR ARE POST LIVER TRANSPLANT (SOLAR-1 & 2 STUDIES)

<table>
<thead>
<tr>
<th>Company</th>
<th>Gilead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>PS099</td>
</tr>
</tbody>
</table>

**Abstract Body**

Background and Aims: Ledipasvir/sofosbuvir (LDV/SOF) with ribavirin (RBV) demonstrated high SVR rates in patients with chronic hepatitis C (HCV) genotype (GT) 1 or 4 infection who have decompensated cirrhosis or who have undergone liver transplantation. Here we evaluated the effect of baseline HCV NS5A and NS5B resistance-associated variants (RAVs) on treatment outcome and characterized the viral resistance in all virologic failures. Methods: Deep sequencing with a 1% assay cut-off was performed for NS5A and NS5B at baseline for all the patients and at the time of virologic failure for those who relapsed. Results: Out of 625, 622, and 619 samples were analyzed for baseline NS5A and NS5B respectively. Table 1 summarizes SVR12 rates by treatment duration and the presence or absence of baseline NS5A RAVs. NS5B RAVs at baseline were uncommon, occurring in 4.8% (28/586) GT1 patients and 3.2% (1/31) GT 4 patients. Of these 29 patients, only one GT1 patient with CPT C cirrhosis who had L159F at baseline and was treated for 24 weeks with LDV/SOF + RBV did not achieve SVR12. NS5A RAVs at positions 24, 28, 30, 31, 58, and 93 were enriched or emerged in 20/22 (91%) GT1 and 1/3 GT4 infected patients with virologic failure. The NS5B NI RAV E237G emerged in 3 GT1a patients and 1 GT4d patient at the time of relapse (4/23, 17%). Conclusions: The presence of baseline NS5A or NS5B RAVs did not impact the treatment outcome to 12 or 24 weeks of LDV/SOF + RBV in GT1 or GT4 HCV patients with liver transplantation without decompensated liver disease, or 24 weeks of LDV/SOF + RBV in patients with decompensated cirrhosis. Lower SVR rates were observed among the limited number of patients with decompensated cirrhosis and baseline NS5A RAVs who received 12 weeks of LDV/SOF + RBV treatment.
PREVALENCE AND IMPACT OF BASELINE RESISTANCE-ASSOCIATED VARIANTS ON THE EFFICACY OF LEDIPASVIR/SOFOSBUVIR OR SIMEPREVIR/SOFOSBUVIR AGAINST GT1 HCV INFECTION: HCV-TARGET INTERIM ANALYSIS

Company: Gilead
Drug: Sofosbuvir
Abstract Number: PS102

Background and Aims: This study aimed to evaluate the prevalence and impact of baseline (BL) resistance-associated variants (RAVs) on ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) or simeprevir/sofosbuvir (SMV/SOF) ± RBV regimens in patients with genotype (GT) 1 HCV infection in HCV-TARGET, a multi-centre, prospective, observational cohort study. Methods: A subset of patients enrolled in HCV-TARGET were consented to serum collection prior to initiating HCV therapy administered according to local standard of care. HCV resistance testing was performed on samples collected before May 12, 2015 using Monogram Biosciences assays (population sequence derived from Illumina MiSeq data with a 10% variant reporting threshold). LDV, SOF and SMV susceptibility was interpreted using Monogram’s rule-based algorithm. Results: BL resistance testing was performed for 486 patients treated with LDV/SOF (n = 209), LDV/SOF + RBV (n = 31), SMV/SOF (n = 186) or SMV/SOF + RBV (n = 60). Demographics included 63% male, 13% Black, 76% GT1a, 52% cirrhosis, 18% with liver transplant, and 55% with prior HCV therapy. The overall prevalence of SMV, LDV and SOF RAVs was 41% (196/480), 24% (116/484) and 2.7% (13/480), respectively. The prevalence of SMV, LDV and SOF RAVs in treatment-naïve (TN) patients (221/486) was 39%, 23%, and 3.2%, respectively, compared to 42%, 25%, and 2.3% in treatment-experienced (TE) patients (265/486). The prevalence of SMV, LDV and SOF RAVs in non-cirrhotic patients (233/486) was 37%, 24% and 2.2%, respectively, compared to 44%, 24% and 3.2% in cirrhotic patients (253/486). To date (403/486 with SVR12 data), 91.3% (368/403) of patients achieved SVR12, and 8.7% (35/403) developed relapse, had no response or had virologic breakthrough. In the LDV/SOF ± RBV cohort (n = 168), 85% (17/20) with LDV or SOF RAVs achieved SVR12, whereas 95% (141/148) without LDV and SOF RAVs achieved SVR12. For the SMV/SOF ± RBV cohort (n = 227), 88% (85/97) with SMV RAVs and 90% (135/150) without SMV RAVs achieved SVR12. Multivariate analysis incorporating RAVs associated with SVR12 for the 486 patient cohort will be presented. Conclusions: SMV, LDV and SOF RAVs at BL for GT1 patients treated with LDV/SOF ± RBV or SMV/SOF ± RBV suggests that the prevalence was generally comparable between TN and TE patients, and between cirrhotic and non-cirrhotic patients.

<table>
<thead>
<tr>
<th>Compound</th>
<th>AA positions associated with resistance analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV</td>
<td>NS3: 36, 80, 122, 155, 168, 170</td>
</tr>
<tr>
<td>LDV</td>
<td>NS5A: 24, 28, 30, 31, 54, 58, 92, 93</td>
</tr>
<tr>
<td>SOF</td>
<td>NS5B: 142, 159, 282, 316</td>
</tr>
</tbody>
</table>
Background and Aims: The once-daily fixed-dose combination (FDC) tablet of sofosbuvir/velpatasvir (SOF/VEL) has demonstrated high efficacy in genotypes 1-6 HCV-infected patients when administered for 12 weeks. We therefore performed a prospective clinical trial to evaluate the safety and efficacy of SOF/VEL in patients coinfected with HCV and HIV-1. Methods: This single arm, open label study enrolled treatment naïve and -experienced HCV/HIV co-infected patients of all HCV genotypes, with or without cirrhosis. Patients who were on stable antiretroviral (ARV) regimens with fully suppressed HIV RNA received SOF/VEL (400 mg/100 mg daily) for 12 weeks. Patients were on a wide range of ARV regimens including emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine with a backbone of raltegravir, cobicistat/elvitegravir, rilpivirine, ritonavir boosted atazanavir, darunavir or lopinavir. Safety evaluations included adverse event (AE) and standard laboratory parameter monitoring in addition to frequent renal function monitoring, CD4 count and HIV-1 RNA levels. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12). Results: A total of 106 patients were enrolled and treated with SOF/VEL for 12 weeks. Overall 86% were male, 45% were black, 77% had IL28B non CC genotypes, 29% had prior treatment failure (primarily PegIFN/RBV), and 16% had compensated cirrhosis. The genotype distribution was 62% GT1a, 11% GT1b, 10% GT2, 11% GT3 and 5% GT4. The median baseline CD4 count was 548 cells/uL (range: 183–1513 cells/uL) with a median estimated glomerular filtration rate of 97 mL/min (range 57–198 mL/min). Boosted protease inhibitor (PI) regimens were the most commonly used regimen (Table 1). In this interim analysis, the most common AEs were fatigue (19%), headache (14%) and nausea (7%). Only one patient experienced a serious adverse event (toe infection) which was considered unrelated to study drugs. No patient experienced confirmed HIV virologic rebound (HIV-1 RNA ≥400 copies/mL). No significant changes in lab abnormalities including renal function were observed. Efficacy and safety outcomes including complete SVR12, HIV parameters and the impact of HCV resistance variants on outcome will be presented. Conclusions: The IFN-free, RBV-free, single tablet regimen of SOF/VEL administered once daily for 12 weeks was well tolerated in HCV/ HIV co-infected patients with GT 1-4, regardless of past treatment experience or presence of cirrhosis.
Background and Aims: Safety and efficacy of Sofosbuvir (SOF) plus Simeprevir (SMV) plus a flat dose Ribavirin (RBV) in elderly patients are very limited. The aim of this study is to analyze efficacy and safety of SMV plus SOF plus a flat dose of RBV (800 mg/day) in a population of HCV genotype 1(G1) elderly patients with compensated liver cirrhosis. Methods: One hundred and seventy-five G1 naive or experienced HCV infected patients with Child Pugh A liver cirrhosis were treated with SOF plus SMV plus a flat dose of RBV. The patients were divided into 2 Group by age: Group I (65 years n = 79). Sustained virological response (SVR) was evaluated 4 (SVR4) and 12 weeks (wks) (SVR12) after end of therapy. Multiple comorbidities, adverse events (AE) and severe adverse events (SAE) were evaluated and compared between the two Groups of patients. Results: Seventy–nine patients were older than 65 years (yrs) (mean 72 ± 5 yrs) while 96 were younger (mean 56 ± 5 yrs). The patients were treated with an association of SOF 400 mg/day plus SMV 150 mg/day plus RBV flat dose (800 mg/day) for a duration of 12 wks. Most were male (52%), caucasian (100%) and treatment experienced (65%) patients. Diabetes was more frequent in Group II patients respect to group I (25.3% vs 13.5% p < 0.03), while systemic hypertension, hypercholesterolemia and cryoglobulinemia had a similar incidence in the two Groups of patients. Hepatocellular carcinoma was more frequent in Group II patients respect to Group I (12.7% vs 1.0% p < 0.002). SVR4 and SVR12 was achieved respectively in 167/175 and 150/158 of total patients. SVR12 was similar between the two Groups of patients (Group I 85/90 patients vs Group II 65/68 patients, p = 0.5). Adverse events (AEs) were similar in the two group of patients except for grade 2 anemia that was more frequent in patients of Group II respect to Group I (31% vs 18% p < 0.05). Grade 3 anemia was similar between the two Groups (Group I 3.1% vs Group II 4.05% p = 0.9). No difference between the two Groups was reported regarding SAE (1% vs 0% ns). Conclusions: SOF plus SMV plus a flat dose of RBV can be used safely in patients aged more than 65 years. Furthermore this regimen presents similar high efficacy in term of SVR12 in the two Groups of patients analyzed.
SIMEPREVIR PLUS SOFOSBUVIR FOR HEPATITIS C VIRUS GENOTYPE 4 INFECTION: A PHASE 3, OPEN-LABEL STUDY

**Company**
Johnson & Johnson

**Drug**
Simeprevir

**Abstract Number**
LBP516

**Abstract Body**
Introduction: The Phase 3, open-label, single-arm PLUTO study (HPC3021; NCT02250807) is investigating the efficacy and safety of 12 weeks of simeprevir (NS3/4A protease inhibitor) + sofosbuvir (NS5B polymerase inhibitor) in treatment-naïve or ([Peg]interferon [IFN] ± ribavirin [RBV])-experienced hepatitis C virus (HCV) genotype (GT)4-infected patients. Material and Methods: Patients received simeprevir 150 mg once daily (QD) + sofosbuvir 400 mg QD for 12 weeks. The primary efficacy endpoint was sustained virologic response 12 weeks after the actual end of treatment (SVR12). Superiority would be confirmed if the lower limit of the SVR12 95% Clopper-Pearson confidence interval (CI) was greater than a historical control rate (a composite of the SVR12 rates from the Phase 3 RESTORE study in HCV GT4-infected patients treated with simeprevir + PegIFN/RBV for each of the subpopulations enrolled). Results are presented from the primary analysis, when all patients reached the SVR12 time point. Results: 40 patients received treatment (male, 29/40 [73%]; mean age, 51 years; IL28B non-CC, 34/40 [85%]; GT4a/4d/4f, 10/40 [25%]/29/40 [73%]/1/40 [3%]; compensated cirrhotic, 7/40 [18%]; median baseline HCV RNA, 6.35 log10 IU/mL [range: 4.8–7.2]; treatment-naïve, 13/40 [33%]; treatment-experienced, 27/40 [68%]; prior relaper, 2/40 (5%); prior non-responder, 21/40 (53%); IFNintolerant, 1/40 (3%)). All 40 patients achieved SVR12 (100% [95% CI: 91, 100]), demonstrating superiority versus the historical control (61%). Adverse events (AEs), all Grade 1 or 2, were observed in 20 (50%) patients. No serious AEs were reported and no patients discontinued study treatment due to AEs. The most frequent AEs (in ≥2 [5%] patients) were headache (20%), asthenia (8%), catarrh (8%), constipation (5%), erythema (5%), and rash (5%). Grade 3 treatment-emergent laboratory abnormalities were confirmed in 2 (5%) patients, each with transient and asymptomatic elevation of pancreatic enzymes. Conclusion: The PLUTO study showed a 100% SVR12 rate with 12 weeks of treatment with simeprevir + sofosbuvir in patients infected with HCV GT4, irrespective of stage of fibrosis or prior treatment with (Peg)IFN ± RBV. The regimen was generally safe and well tolerated.
Background and Aims: The treatments of hepatitis C in liver transplant patients until recently, had low efficacy and many adverse effects. The new direct acting antivirals Simeprevir (SIM) and sofosbuvir (SOF) have significantly increased the efficacy and safety of treatment in liver transplant hepatitis C patients genotype 1. The aim of this study was to determine the efficacy and safety in real life of the combination SOF + SIM ± RBV in a group of liver transplant patients genotype 1. Methods: This is a multicenter, retrospective study including 232 genotype 1 hepatitis C liver transplant patients treated with SIM + SOF ± RBV from 21 Liver transplant Centres. Efficacy and safety data, and mortality rate were assessed. Results: The majority of patients were male (73.7%) and the average age was 61.49 ± 8.9 years. The 63.1% were Ile 28B CT and the genotype 1a was 15.02%. The 59.05% of patients have been previously treated, the most part with interferon based therapy, but 10.8% with IP and the 4.3% with SOF. The 51.14% were null responders. There was a 53.8% of patients with fibrosis 4. The MELD score average was 8.86 ± 2.87 (6–24). In the 60.34% of the patients RBV was included in the treatment. The majority of the patients were treated during 12 weeks (86.63%). At the end of treatment (EOT), all patients had undetectable serum HCV-RNA but one patient had to stop the treatment for liver and kidney impairment. The rates of sustained virological response (SVR) 4 and 12 were 97.28% and 93.75%, respectively. The SVR 12 in cirrhotic patients was 92.4% versus 95.34 in non cirrhotics, and SVR 12 in RBV treated patients was 95.7% versus 90.9%. Treatment was well tolerated and the mortality rate was 1.3% no treatment related Conclusions: The treatment of HCV genotype 1 patients after liver transplantation, with Simeprevir plus sofosbuvir in real life, is a very effective and safe option even in post-transplant liver cirrhosis The mortality rate was very low and no drug-related.
Background and Aims: Simeprevir (SMV) is a hepatitis C virus (HCV) protease inhibitor approved as part of a combination antiviral regimen to treat non-transplant patients with chronic hepatitis C genotype 1 infection. Methods: This is an ongoing, prospective, partially-randomised, phase 2, open-label study of once-daily SMV 150 mg + sofosbuvir (SOF; HCV nucleotide polymerase inhibitor) 400 mg with and without ribavirin (RBV) 1000 mg (1200 mg for subjects ≥75 kg) in subjects with recurrent genotype 1 HCV post-orthotopic liver transplant; the primary endpoint was the proportion of subjects with wk 12 sustained virologic response (SVR12). Choice of immunosuppression was at the investigator’s discretion, excluding cyclosporine due to the drug interaction with SMV. The first 33 subjects without cirrhosis were randomised 1:1:1 into three arms and stratified by genotype subtype and presence of Q80K: 1) SMV + SOF + RBV ×12 wks, 2) SMV + SOF ×12 wks, and 3) SMV + SOF ×24 wks; 13 additional subjects (2 with, 11 without cirrhosis) were enrolled in the SMV + SOF 24-wk arm. An interim analysis was performed when all subjects in the 12-wk arms reached the SVR12 timepoint. The final analysis (including pharmacokinetics) will be presented at the congress.

Results: All 46 subjects received at least one dose of study drug; median age, 60 y; 74% male; 80% white; mean (standard deviation) baseline HCV RNA level, 6.4 (0.8) log10 IU/mL; 72% genotype 1a (three subjects/arm had Q80K). Median time since liver transplant was 4.5 y. At the time of analysis, five subjects in the 24-wk arm (without cirrhosis) and 22 subjects in the 12-wk arms had reached the SVR12 timepoint; 93% (25/27) achieved SVR12 (82% in RBV arm and 100% in arms without RBV). Two subjects did not achieve SVR12 (one had viral relapse at follow-up wk 4, one did not have wk 12 data [death by suicide]; both were in the RBV arm). Four (9%) subjects had a serious adverse event, considered unrelated to treatment per investigator. No episodes of acute rejection were reported. Conclusions: In liver transplant recipients with recurrent HCV infection, SMV + SOF treatment for 12–24 wks with or without RBV resulted in a high SVR12 rate (93%) and was well tolerated; SVR12 was achieved by 100% of subjects with available data in both SMV + SOF arms without ribavirin, suggesting that 12 wks of SMV + SOF therapy is adequate for genotype 1 liver transplant subjects without cirrhosis.
**CONSISTENT SIMEPREVIR RESISTANCE PROFILE IN HEPATITIS C VIRUS GENOTYPE 1-INFECTED PATIENTS FAILING SIMEPREVIR INTERFERON-FREE COMPARED WITH INTERFERON-CONTAINING REGIMENS**

<table>
<thead>
<tr>
<th>Company</th>
<th>Johnson &amp; Johnson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Simeprevir</td>
</tr>
<tr>
<td>Abstract</td>
<td>THU-214</td>
</tr>
<tr>
<td>Number</td>
<td></td>
</tr>
</tbody>
</table>

**Abstract Body**

Background and Aims: In addition to peginterferon and ribavirin (PR), simeprevir (SMV) is approved with sofosbuvir (SOF) and evaluated as part of other interferon (IFN)-free combinations for treating chronic hepatitis C virus (HCV) infection. HCV genotype (GT)1 patients failing SMV/PR generally had emerging NS3 resistance-associated variants (RAVs) which became undetectable after treatment. Here, emerging NS3 RAVs in GT1 patients failing SMV IFN-free regimens are evaluated. Methods: HCV NS3 Sanger sequencing was performed at time of failure and last study visit for the 53 GT1 patients with virologic failure in the SMV/SOF COSMOS and OPTIMIST-1/-2 studies. In vitro SMV susceptibility was assessed in a transient replicon assay as site-directed mutants or chimeric replicons with patient-derived NS3 protease sequences. Results: The majority (21/26; 80.8%) of GT1 patients failing 12-/24-week SMV/SOF regimens, mainly due to viral relapse, had emerging NS3 RAVs. Among the 20 GT1a patients, R155K emerged alone or combined with D168E and/or I170T in 6 patients with and 2 without baseline Q80K; D168E emerged alone in 4 patients with Q80K and combined with I170T in 1 patient without Q80K; I170T emerged alone in 1 GT1a patient with Q80K while Q80R and D168A each emerged alone in 1 GT1a patient without Q80K. Among the 6 GT1b patients, D168V and D168A emerged alone in 4 and 1 patients, respectively. The NS3 RAVS at time of failure generally conferred highlevel resistance to SMV in vitro. Two of the 27 (7.4%) patients relapsing after 8 weeks’ SMV/SOF had emerging NS3 RAVs; R155K and I170T emerged alone each in 1 GT1a patient with Q80K. The median follow-up time for the 23 patients failing SMV/SOF with NS3 RAVs was 16.3 weeks compared with 28.4 weeks for patients failing SMV/PR. For 2/23 patients, both GT1b, emerging D168A and D168V were no longer detected after 12.6 and 20.0 weeks, respectively. This was similar to the time to return to wildtype for the respective mutations emerging in patients failing SMV/PR. For the 21 patients who still had emerging RAVs detected at the last study visit, the follow-up time was too short. Conclusions: NS3 RAVs emerging in patients failing SMV IFN-free regimens were similar to those observed in patients failing SMV/PR. The consistent SMV resistance profile suggests a similar pattern of disappearance of emerging NS3 RAVs after IFN-free treatment, but follow-up time was overall too short to confirm. Funding: Janssen Research & Development.
DEEP SEQUENCING RESULTS FROM THE PHASE 2 IMPACT STUDY OF SIMEPREVIR IN COMBINATION WITH DACLATASVIR AND SOFOSBUVIR IN TREATMENT-NAÏVE AND -EXPERIENCED PATIENTS WITH CHRONIC HEPATITIS C VIRUS GENOTYPE 1 OR 4 INFECTION AND DECOMPENSATED LIVER DISEASE

**Company**  
Johnson & Johnson

**Drug**  
Simeprevir

**Abstract Number**  
THU-215

**Abstract Body**  
Background and Aims: The Phase 2, open-label IMPACT study (NCT02262728) is investigating 12 weeks of simeprevir (NS3/4A inhibitor; 150 mg once daily), daclatasvir (NS5A inhibitor; 60mg once daily) and sofosbuvir (NS5B inhibitor; 400 mg once daily) in patients with hepatitis C virus (HCV) genotype 1/4 infection and decompensated liver disease. Deep sequencing assessed the presence of pretreatment resistance-associated variants. Methods: Deep sequencing of HCV NS3, NS5A and NS5B genes was performed on the Illumina MiSeq platform (1% detection limit). In addition, population sequencing data of the same genes were available at baseline for all 40 patients (26 genotype 1a, 13 genotype 1b, 1 genotype 4). Amino acid substitutions at NS3 positions 43, 80, 122, 155, 156 and 168; NS5A positions 28, 30, 31, 32 and 93; and NS5B positions 96, 142, 159, 282, 316, 320, 321, 390 and 415 were considered. Among these, the analysis focused on resistance-associated variants defined as substitutions associated in vitro with simeprevir, daclatasvir or sofosbuvir fold change in 50% effective concentration compared with wild type >2. Results: Deep sequencing confirmed the results from population sequencing and additional resistance-associated variants were observed with quasispecies frequencies ranging from 1–13%. By deep sequencing, 42% (16/38), 13% (5/39) and 0% (0/39) of patients carried baseline resistance-associated variants at positions of interest in NS3, NS5A and NS5B, respectively. 32% of patients carried simeprevir resistance-associated variant Q80K (12/38; all genotype 1a; all at 100% variant frequency), 11% had Q80R (4/38; 2 genotype 1a, 2 genotype 1b; variant frequency 1–99%) and 3% had F43L (1/38; genotype 1a; variant frequency 13%). Daclatasvir resistance-associated variant Y93H was observed in 10% (4/39; all genotype 1b; variant frequency 1–98%) of patients; Q30R and Y93C were seen in 1 patient each (3%; in a 1a and 1b patient, at 1% and 4% variant frequency, respectively). All patients carried resistance-associated variants in 1 gene only, except for 1 genotype 1b patient carrying both Q80R in NS3 and Y93H in NS5A. All (100%) patients achieved sustained virologic response at follow-up Week 12 (SVR12). Conclusions: In the IMPACT study, NS3 or NS5A resistance-associated variants were detected by deep sequencing in 42% and 13% of patients, respectively. All patients achieved SVR12, regardless of the presence of baseline NS3 and/or NS5A resistance-associated variants.
TREATMENT WITH SOFOSBUVIR + SIMEPREVIR FOR 12 WEEKS IN HCV COMPENSATED CIRRHOSIS (GENOTypes 1 AND 4); THE USE OF RIBAVIRIN DOES NOT INFLUENCE SUSTAINED VIRAL RESPONSE

Company | Johnson & Johnson
Drug | Simeprevir

Abstract Number | SAT-103

Abstract Body
Background and Aims: The COSMOS study reported a high rate of sustained viral response (SVR) with Sofosbuvir + Simeprevir ± Ribavirin in patients with advanced liver fibrosis; however the number of cirrhotic patients included was small. Our aim was to assess the efficacy and safety of this therapeutic combination in patients with compensated cirrhosis. Methods: We analyze the outcome of our patients with HCV genotype 1 and 4 infection treated with Sofosbuvir + Simeprevir ± Ribavirin during the last year. The decision about use Ribavirin or not was a personal choice of the prescriber. The presence of Q80K polymorphism in HCV-genotype 1a infection was not explored in our patients. Cirrhosis (Stage 4 fibrosis) was defined by a transient elastography result ≥14 Kpascal. Results: A total of 79 patients were treated (45 Men/34 Women; mean age: 58.9 ± 9.9 years). Sixty-nine patients (87.3%) had cirrhosis. Baseline characteristics were: Child-Pugh A 89.9%; MELD 7.72 ± 1.9; Presence of esophageal varices 40.5%; History of hepatic decompensation 13.9%; and previous hepatocellular carcinoma 10%. Patients had infection by HCV-Genotype 1b/1a/4: 67.1%/21.5%/8.9% and they were naïve 32.9%, Relapers 13.9%, Partial responders 8.9%, and Null responders 39.2%. Among cirrhotic patients Ribavirin was added to Sofosbuvir + Simeprevir in 49.2% and SVR was similar with and without Ribavirin (93.5% vs 88.8%, p = 0.65). In patients with cirrhosis SVR-4 was 93.7% and SVR-12 was 91.4%. No significant differences in SVR-12 were observed between patients treated with or without Ribavirin according to HCV-genotype or previous treatment response. SVR- 12 with and without RBV in genotype 1a (n = 12/2) was 100% vs 100%, in genotype 1b (n = 13/25) was 84.6% vs 88%; All patients with genotype 4 (n = 5) were treated with Ribavirin and reached SVR-12 (100%). SVR-12 with or without Ribavirin was 91.6% vs 83.3% in naïves (n = 12/6), 100% vs 100% in relapers and partial responders (n = 6/5), and 90.9% vs 85.7% in null responders (n = 11/14). Three patients (3.8%) suffered severe adverse events, including one death and one discontinuation of therapy. Patients treated with Ribavirin presented a higher number of mild adverse events. Conclusions: 1) Treatment of compensated cirrhosis with Sofosbuvir + Simeprevir with or without Ribavirin reached a SVR- 12 of 91.4%. 2) Cirrhotic patients treated without Ribavirin achieved similar SVR-12 than those treated with Ribavirin.
TREATMENT OF HCV WITH SIMEPREVIR ASSOCIATED TO DACLATASVIR IN PATIENTS WITH STAGE 4 AND 5 CHRONIC RENAL FAILURE

Company: Johnson & Johnson

Drug: Simeprevir

Abstract Number: SAT-123

Abstract Body: Background and Aims: HCV treatment with direct acting antivirals in patients with severe chronic renal failure (CRF) is conditioned by the fact that the Sofosbuvir is contraindicated in patients with glomerular filtration rate (GFR) <30 mL/min/1.73 m2. Another poor studied association may be considered in this setting. Objective: To study the efficacy and tolerability of Simeprevir and Daclatasvir (SIM + DAC) combination in patients with GFR <30. Methods: A prospective, observational study including all patients with HCV and GFR <30 treated with SIM + DAC ± Ribavirin (RBV) in our center. CRF is defined as stage 4 if GFR between 29–15 and stage 5 if GFR <14 and/or dialysis. Results: We included 21 monoinfected patients, 11 men, with a mean age of 57 years. Fibrosis: 6 patients F0-1, 1 F2, 3 F3 and 11 F4. Cirrhotic: 4 were compensated and 7 descompensated; 6 were Child - Pugh A and 5 B; mean MELD of 14.5 (range 11–19). Of the 21 patients, 11 had a functioning graft: 7 liver, 3 kidney and 1 heart. CRF stage: 9 stage 4 and 12 stage 5; 10 were on dialysis. HCV genotype: 2 patients 1a, 17 1b, one was 4 and one was infected by 1a + 1b; the mean viral load was 5,162,920 IU/mL. Sixteen patients had received previous antiviral treatment: 4 standard IF ± RBV, 10 pegylated IF + RBV and 2 pegylated IF + RBV + Telaprevir, all but one were non-responders. Nine patients were treated for 12 weeks, 6 with SIM + DAC + RBV and 3 with SIM + DAC. Ten patients were treated for 24 weeks with SIM + DAC. In two patients antiviral was discontinued at week 8 by increasing the RNA. In terms of efficacy, sustained viral response (SVR) was 86.6% (13/15). Of the remainder, a patient has a viral response within a week + 4 and 5 have reached the end of treatment, 4 with undetectable RNA and one with detectable but not quantifiable RNA. The most common side effect was anemia that led to transfusion in 7 patients and erythropoietin in 11 (although 9 patients were already receiving erythropoietin before the start of antiviral); in 2 cases RBV was retired and extended treatment to 24 weeks. Antivirals were not withdrawn due to side effects. Conclusions: 1 – Association SIM + DAC + RBV is a good therapy in patients with HCV and CRF with GFR <30 with an SVR of 86.6%. 2 – The main side effect is anemia requiring changes in the regimen but not the withdrawal of antivirals. 3 – The SIM + DAC + RBV association must be considered in the therapeutic arsenal of a population with few alternatives for the treatment of HCV.
Efficacy and Tolerability of Simeprevir and Daclatasvir for 12 or 24 Weeks in HCV Genotype 1B-Infected Treatment-Naïve Patients with Advanced Fibrosis or Compensated Cirrhosis

Company: Johnson & Johnson

Drug: Simeprevir

Abstract Number: SAT-130

Abstract Body: Background and Aims: Simeprevir (SMV) and daclatasvir (DCV) are approved, widely available direct-acting antivirals (DAAs). This combination of therapies warrants further investigation in HCV GT1b, as does the effect of baseline NS5A RAVs. We describe interim data from an ongoing Phase 2 study investigating the efficacy and safety of SMV + DCV in HCV GT1b.

Methods: The open-label COMMIT study included patients with chronic HCV GT1b infection (≥18 years; treatment-naïve; G1b; advanced fibrosis or compensated cirrhosis [METAVIR F3/4]; no restriction on age or body mass index [BMI]). Patients harboring NS5A-Y93H and/or L31M/V RAVs at screening (population sequencing) were excluded. SMV (150 mg) + DCV (60 mg) once daily was administered for 12 weeks; patients could extend treatment to 24 weeks at investigator discretion. The primary efficacy endpoint is sustained virologic response after 12 weeks (SVR12). This interim analysis was conducted when all patients had reached study Week 16. HCV RNA was quantified with the Roche Ampliprep assay (LLOQ = 15 IU/mL; LOD = 15 IU/mL).

Results: Of 151 patients screened, 23 (15%) were excluded due to NS5A variants (Y93H or L31M/V) and 106 (70%) were treated (for demographics, see Table). 42/106 (40%) patients received 12 weeks’ treatment; 64/106 (60%) extended treatment to 24 weeks. Amongst patients receiving 12 weeks’ treatment (ITT), 37/42 (88%) achieved SVR4; of those who did not achieve SVR4, four experienced viral breakthrough (VBT) and one withdrew consent. In the 24-week group, three patients experienced virologic failure, all due to VBT. Characteristics of patients (n = 7) experiencing VBT included male gender (n = 2/7), baseline HCV RNA ≥6,000,000 IU/mL (n = 3/7); IL28B CT|TT genotype (n = 4;3/7); METAIVIR F4 (n = 4;7), IFN-ineligibility (n = 2;7). VBT occurred at Week 4 (n = 3), Week 8 (n = 1), Week 12 (n = 2) and Week 16 (n = 1). Two (2%) patients discontinued treatment due to AEs that were not deemed related to SMV + DCV; 74 (70%) experienced any AE; 6 (6%) ≥1 SAE (of which 1 was considered possibly related to SMV + DCV); 7 (7%) ≥1 Grade 3/4 AE (of which 3 were considered related to SMV + DCV).

Conclusions: SMV + DCV demonstrated strong antiviral activity: among patients treated for 12 weeks, 88% achieved SVR4. However, VBT occurred in four patients in the 12-week group and three patients in the 24-week group. SMV + DCV was well tolerated in this patient population with advanced liver disease. Full SVR12 and resistance analysis will be presented.
Background and Aims: Several direct-acting antiviral combinations are recommended for the treatment of genotype 1 (G1) chronic hepatitis C (CHC) patients. Simeprevir (SMV) and sofosbuvir (SOF) with or without ribavirin (RBV) has been shown to be highly efficient in some clinical trials. This study was conducted to assess the effectiveness and safety of this regimen in real-world patients with G1 CHC. Methods: A multicenter study was performed including 115 patients with G1 CHC who were undergoing a SMV-SOF combination for 12 weeks (with or without RBV at their doctor’s discretion). Variables analyzed: age, sex, BMI, genotype, subtype, basal fibrosis (transient elastography), presence of cirrhosis (>12.5 kPa and/or biopsy F4 and/or ultrasound diagnosis), analytical parameters, previous treatment experience, RBV use and the 12-week post-treatment sustained virological response (SVR12). Results: Baseline characteristics: 78 (68%) males, mean age of 57.6 ± 9.6 years, BMI of 25 (18–47) and G1 subtypes 1a and 1b were found in 26 (23%) and 83 (73%) of the patients, respectively. HCV-RNA was 1,080,000 UI/mL (11,390–17,000,000). The CC, CT and TT polymorphisms of the IL28 (n = 95 patients) were observed in 11%, 74% and 16% of the patients, respectively. The platelet count was 128,000/mm3 (13,200–347,000); the ALT value was 61 UI/mL (10–330); the assessment of fibrosis was 17.3 (4.4–75) kPa with cirrhosis in 93 (82%) patients. Treatment-experienced and treatment-naïve patients were 88 (77%) and 27 (23%), respectively. 60 of the treatment failures occurred with pegylated interferon and RBV and 28 with telaprevir or boceprevir associated. The global SVR12 rate was 91% (105/115 patients). The SVR was 90% without RBV and 92% with RBV (p = 0.7). The SVR12 observed in subgroups of patients treated with/without RBV was: cirrhotic patients, 91%/88% (p = 0.7); non-cirrhotic patients, 100%/100%; subtype 1a, 93%/100% (p = 1); subtype 1b, 91%/83% (p = 0.4); treatment-naïve, 90%/88% (p = 1); and treatment-experienced, 93%/91% (p = 0.67). None of the cases required discontinuation of the treatment due to adverse events. Conclusions: High rates of SVR12, over 90% globally, were observed in this study of G1 CHC patients (more than 80% cirrhotic) undergoing a treatment with SMV and SOF. Non-significant differences in SVR12 rates were observed when RBV was added. Interruption of the treatment was not required due to the lack of side effects.
Background and Aims: Egypt has high prevalence of chronic HCV infection, more than 90% of patients are infected with genotype 4 and 22% of patients receiving ribavirin developed anaemia. This represents an urgent need for safe and highly effective and safety of one of interferon-free regimens; sofosbuvir (NS5B inhibitor) in combination with simeprevir (NS3/4A protease inhibitor) in Egyptian chronic HCV patients. Methods: This is a prospective, observational study started June 2015 in four centres affiliated to the National Committee for the control of Viral Hepatitis in Egypt. Key inclusion criteria were age 18–70 years, evidence of chronic HCV infection for more than 6 months, positive HCV RNA by PCR, and absence of decompensated cirrhosis or other causes of liver disease. All patients (whether treatment naïve or treatment experienced; cirrhotics or not) received sofosbuvir (Sovaldi, Gilead Sciences) 400 mg plus simeprevir (OLYSIO, Janssen Therapeutics) 150 mg daily for 12 weeks without ribavirin. The primary end point was a sustained virologic response at 4 (SVR4; defined as HCV RNA < LLD at 4 weeks post-treatment) and 12 (SVR12; HCV RNA < LLD at 12 weeks post-treatment) weeks after the end of therapy. Results: Out of 570 patients enrolled, 217 reached 4 weeks post treatment (SVR4) at the time of this abstract. Of those 217 patients: 174 (80.2%) were treatment-naïve and 43 (19.8%) treatment-experienced. 154 (71%) were male, 89 (41.01%) cirrhotic. End of treatment response was 99% (215/217) with only two patients were treatment failures (one naive cirrhotic and the other was treatment-experience non cirrhotic). To date, 207 out of 215 patients had HCV RNA < LLD (SVR4 = 96.3%). The other 8 patients who relapsed; 6 were cirrhotics (one of them was treatment experienced) and 2 were treatment experienced non cirrhotic. Overall sofosbuvir and simeprevir were well tolerated; most adverse events (AEs) were mild or moderate in severity. No Serious AEs. The most frequent AEs (>30% of patients) were consistent with the known side effects of sofosbuvir and simeprevir (fatigue, headache, pruritis and indirect hyperbilirubinemia). Skin rash was rare. By EASL time, more SVR4 and SVR12 data will be presented. Conclusions: Sofosbuvir plus simeprevir without ribavirin for 12 weeks proved to be a simple, effective, and well-tolerated, interferon free regimen in Egyptian patients with chronic HCV regardless of previous treatment or underlying cirrhosis.
EFFECTIVENESS OF SIMEPREVIR TREATMENT FOR HEPATITIS C IN REAL PRACTICE: PRELIMINARY RESULTS FROM THE STILY ITALIAN OBSERVATIONAL STUDY

Company: Johnson & Johnson

Drug: Simeprevir

Abstract Number: SAT-162

Abstract Body:
Background and Aims: Simeprevir associated with Sofosbuvir with or w/o Ribavirin has been the first highly effective regimen available to treat HCV GT1 and GT4 patients in Italy. STIly is an ongoing observational multicenter cohort study enrolling Italian patients with CHC designed to evaluate the effectiveness and safety of Telaprevir or Simeprevir-based regimens in routine practice. Here we report the preliminary results about effectiveness of Simeprevir on 338 patients. Methods: The STIly study involved 46 sites across Italy, consecutively recruiting patients from June 2014 to September 2015. By protocol, enrolled patients were men or women aged 18 years or more, chronically infected by GT1 or GT4 HCV. Population included naïve or treatment experienced patients, with or w/o cirrhosis. Effectiveness of Simeprevir was evaluated by means of Sustained Viral Response 4 or more weeks after treatment end (SVR4+), which was defined as undetectable serum HCV RNA levels 4–12 weeks (or up to 16 weeks) after treatment end. Results: Out of 349, 338 had data available for preliminary analysis. Baseline characteristics of the 338 evaluable patients were: 226 (67%) males, mean (SD) age was 58.5 (10.2) years; 276 (82%) genotype 1, of whom 91 and 185 were 1a and 1b, respectively; 62 (18%) were genotype 4; 264 (78%) with cirrhosis. Naïve patients were 136 (40%) and treatment experienced were 202 (60%). Null responders to previous treatment were 107 (32%). Regimens were: Simeprevir / Sofosbuvir (N = 78) and Simeprevir/Sofosbuvir + Ribavirin (N = 260). SVR4+ was achieved in 209 (87%) out of 239 evaluable patients, namely in 161/187 (86%) and 48/52 (93%) patients in Simeprevir / Sofosbuvir with and w/o Ribavirin, respectively. Table 1 reports SVR4+ stratified by treatment regimens and clinical features. Conclusions: Overall, 87% of patients undergoing Simeprevir with Sofosbuvir +/- Ribavirin achieved SVR4+. Addition of ribavirin appeared useful only in genotype 1a patients, although to be validated in the final analysis. This preliminary analysis of real life practice in Italy validates effectiveness of SMV based regimens as it emerged in registration studies.

<table>
<thead>
<tr>
<th>Table: SVR4+ stratified by treatment regimens and clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMV SOF</strong></td>
</tr>
<tr>
<td><strong>(n=48)</strong></td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Cirrhosis (F4)</td>
</tr>
<tr>
<td>Naïve</td>
</tr>
<tr>
<td>Treatment Experienced</td>
</tr>
<tr>
<td>Genotype 1a</td>
</tr>
<tr>
<td>Genotype 1b</td>
</tr>
<tr>
<td>Genotype 4</td>
</tr>
</tbody>
</table>
EFFECTIVENESS OF SIMEPREVIR-CONTAINING REGIMENS AMONG PATIENTS WITH CHRONIC HEPATITIS C VIRUS IN VARIOUS US PRACTICE SETTINGS: THE SONET STUDY

Company  
Johnson & Johnson

Drug  
Simeprevir

Abstract Number  
SAT-167

Abstract Body  
Background and Aims: Simeprevir (SMV) is an oral, once-daily, hepatitis C virus NS3/4A protease inhibitor approved for the treatment of chronic hepatitis C virus (HCV) infection as part of combination antiviral therapy. The SONET study evaluates the real-world effectiveness of SMV-containing regimens. Methods: SONET is an ongoing, observational, US-based study. Eligible patients are aged ≥18 y with chronic HCV genotype 1 infection and without prior direct-acting antiviral exposure. Patients received a SMV-containing regimen per routine clinical practice; treatment decisions were at healthcare provider discretion. Primary endpoint was post-treatment wk 12 sustained virologic response (SVR12); secondary endpoints included patient characteristics, treatment exposure, healthcare resource utilization, practice setting types, virologic failure, and safety. This interim analysis was conducted when ≥300 patients had wk 12 on-treatment results. The final analysis, including assessment of single and multiple prognostic factors associated with SVR12, will be presented at the congress. Results: At the time of data cutoff for this interim analysis, 315 patients were enrolled and dosed with SMV; 291 (92%) had completed treatment. The cohort has: median age, 58 y; 63% (n = 199) male; 61% (n = 191) white; 34% (n = 108) black; 15% (n = 46) Hispanic/Latino; 72% (n = 226) genotype 1a; 21% (n = 67) genotype 1b. Overall, 92% (n = 291) received SMV + sofosbuvir (SOF); 5% (n = 17) SMV + SOF + ribavirin (RBV); 2% (n = 7) SMV + peginterferon (PEG) + RBV. The distribution of subjects at practice settings was: academic medical center, 20% (n = 62); private practice, 63% (n = 199); integrated health network, 10% (n = 31). At baseline, 30% (n = 95) were treatment-experienced; 39% (n = 124) had cirrhosis; 13% (n = 41) had hepatic decompensation. 1% (4/311) reported having 8–14 drinks/wk and 13% (39/311) having <8 drinks/wk; 25% (78/311) annual household income <$10,000 US dollars. 124 patients with cirrhosis and 191 patients without cirrhosis received SMV for a median duration of 12 weeks. Virologic response data are shown (Table). Most common adverse events (AEs) were headache (13%), fatigue (13%), and nausea (11%); 9% of patients had a serious AE, none were related to SMV treatment. Conclusions: In this analysis, use of SMV + SOF was common and 92% of patients on this regimen (excluding non-virologic failures) achieved SVR12. SMV-based treatment was well tolerated in this heterogeneous US population, including patients with cirrhosis and hepatic decompensation.
SAFETY OF SIMEPREVIR-BASED TREATMENT FOR HEPATITIS C IN REAL PRACTICE: PRELIMINARY RESULTS FROM THE STILY OBSERVATIONAL STUDY

Company  Johnson & Johnson  
Drug  Simeprevir  
Abstract Number  SAT-212  
Abstract Body  Background and Aims: Simeprevir associated with Sofosbuvir with or w/o Ribavirin has been the first highly effective regimen available to treat HCV GT1 and GT4 patients in Italy. STIly is an ongoing observational multicenter cohort study enrolling Italian patients with CHC designed to evaluate the effectiveness and safety of Telaprevir or Simeprevir-based regimens in routine practice. Here we report safety data of Simeprevir-based regimens on 338 real life patients. Methods: The STIly study involved 46 sites across Italy, consecutively recruiting patients from June 2014 to October 2015. By protocol, enrolled were men or women aged 18 years or more chronically infected by GT1 or GT4 HCV. Results: Out of 349 patients enrolled, 338 had data available for preliminary analysis. 226 (67%) were males, mean (SD) age 58.5 (10.2) years, 54 (16%) aged >=70. There were 276 HCV GT1 patients (82%), 91 and 185 1a and 1b, respectively; 62 (18%) had GT4; 264 (78%) had cirrhosis; 183 patients had comorbidities, 63 were HIV-positive, 11 underwent liver transplant before therapy start. 78 received Simeprevir/Sofosbuvir (SMV/SOF), 260 Simeprevir/Sofosbuvir + Ribavirin (SMV/SOF + R); 22 patients were included in a compassionate use program. 98 (29%) had at least one AE of which 57 (31%) were aged less than 60 years, 30 (30%) between 60 and 70 and 11 (20%) were older than 70 years. Overall, 188 AEs were observed (Table 1). 31 AEs occurred in 18 (23%) receiving SMV/SOF, whereas 157 AEs occurred in 80 (31%) patients receiving SMV/SOF + R: for 2 and 27 of which Ribavirin was interrupted or down dosed, respectively, and SOF increased in 1. SAEs occurred in 4 patients (1.4%): 1 SMV/SOF, 3 in SMV/SOF + R (1 related to treatment). Conclusions: This preliminary analysis of real life practice in Italy validates safety of SMV based regimens as it emerged in registration studies. The study is sponsored by Janssen-Cilag SpA.
Background and Aims: Traditional management of acute HCV with peg IFN α2b and weight based RBV has had equivocal success with high SVR rates but significant adverse effects. Oral DAA’s have achieved SVR rates exceeding 95% in many cohorts and offer significant advantages particularly in vulnerable populations such as acute HCV. This clinical pilot study evaluates the efficacy of Sofosbuvir (SOF) with Ledipasvir (LDV) or Simeprevir (SIM) in acute Hepatitis C. Methods: 29 patients with a diagnosis of acute hepatitis C (negative past HCV antibody + new onset HCV RNA) were recruited from 6 inner city drug rehabilitation programs in Brooklyn, NY. They were divided into 2 groups; Group A (n = 14): SOF 400 mg + LDV 90 mg (daily once) – 4 weeks Group B (n = 15): SOF 400 mg + SIM 150 mg (daily once) – 8 weeks Labs: Prior to therapy HCV: RNA 0 and 12 weeks, sickle cell panel, LFT’s, CBC, Chem profile. On therapy HCV: RNA on day 0, 1 week, 4 week, 8 week followed by 16th week (SVR12 Group Group A) and 20th week (SVR12 Group B), LFT’s, CBC, Chem profile

Conclusions: This study demonstrates a high SVR with a very short course DAA’s in acute Hepatitis C. Both the groups achieved overall 93% without breakthrough or relapse. Overall the drugs were well tolerated with minimal side events. Larger trials will validate the efficacy and short treatment paradigm.
PHARMACOKINETIC INTERACTIONS BETWEEN SIMEPREVIR AND LEDIPASVIR IN TREATMENT-NAÏVE HEPATITIS C VIRUS GENOTYPE 1-INFECTED PATIENTS WITHOUT CIRRHOSIS TREATED WITH A SIMEPREVIR/SOFOSBUVIR/LEDIPASVIR REGIMEN

Company: Johnson & Johnson

Drug: Simeprevir

Abstract Number: SAT-264

Abstract Body: Background and Aims: The drug interaction between simeprevir (NS3/4A protease inhibitor) and ledipasvir (NS5A replication complex inhibitor) was investigated in treatment-naïve hepatitis C virus genotype 1-infected patients without cirrhosis, treated with simeprevir/sofosbuvir/ledipasvir in a Phase 2, open-label study (NCT02421211). Methods: Patients (N = 40) were randomised to 1 of 2 panels (n = 20 in each). Panel 1: patients received simeprevir 150mg and sofosbuvir 400mg once daily from Day 1–Day 14. From Day 15–Day 70, patients received simeprevir 150mg and ledipasvir/sofosbuvir 90/400 mg once daily. Panel 2: patients received ledipasvir/sofosbuvir 90/ 400mg once daily from Day 1–Day 14. From Day 15 – Day 56, patients received simeprevir 150 mg and ledipasvir/sofosbuvir 90/400 mg once daily. Total treatment duration in Panel 1 and Panel 2 was 10 weeks and 8 weeks, of which 8 and 6 weeks, respectively, were with simeprevir + ledipasvir/sofosbuvir. The plasma concentration versus time profiles of simeprevir in the presence or absence of ledipasvir (Panel 1: Day 28 versus Day 14) and of ledipasvir in the presence or absence of simeprevir (Panel 2: Day 28 versus Day 14) were assessed. Safety data up to Day 28 are reported. Results: Baseline characteristics: male, 45%; genotype 1a/1b, 20/ 80%; NS3/NS5A resistance-associated variants, 8/20%; no NS5B S282T was observed at baseline. The maximum plasma concentration and area under the plasma concentration-time curve during the dosing interval were, respectively, 2.45- and 3.13-fold higher, for simeprevir with versus without ledipasvir (Panel 1); 1.60- and 1.70-fold higher, for ledipasvir with versus without simeprevir (Panel 2), based on least squares means ratios. Adverse events (AEs) occurred in 73% (29/40) of patients; all Grade 1/2 and the most common was photosensitivity (33%). No serious AEs or treatment discontinuations due to AEs were reported. Grade 3 treatment-emergent laboratory abnormalities were observed in Panel 1 (n = 2; pancreatic amylase elevation and hyperbilirubinemia). Sustained virologic response 12 weeks after the end of treatment will be presented. Conclusions: The combination of simeprevir and ledipasvir, in the presence of sofosbuvir, led to no clinically significant increase in ledipasvir and a moderate increase in simeprevir plasma concentrations, respectively. The safety profile was similar to that of the single drugs; however, photosensitivity was reported more frequently. Funding: Janssen
### SAFETY AND EFFICACY OF SOFOSBUVIR PLUS SIMEPREVIR IN A SPANISH COHORT OF 622 CIRRHOTIC PATIENTS INFECTED WITH GENOTYPES 1 OR 4

<table>
<thead>
<tr>
<th>Company</th>
<th>Johnson &amp; Johnson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Simeprevir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>SAT-286</td>
</tr>
</tbody>
</table>

#### Abstract Body

Background and Aims: The combination of Sofosbuvir (SOF), a polymerase inhibitor, plus Simeprevir (SMV), a protease inhibitor (PI), with or without ribavirin (RBV), has shown a good efficacy and safety profile in compensated cirrhotic patients infected with the hepatitis C virus (HCV) genotype (GT) 1 or 4. To date, there is no available data regarding the efficacy of this combination in real-life cirrhotic patients in Spain. The aim of this multicentric study was to assess the Spanish clinical experience using SOF/SMV (±RBV) in a large cohort of real-life compensated cirrhotic patients. Methods: Retrospective analysis of data from GT1 and GT4 infected cirrhotic patients treated with this oral antiviral combination. Results: Six-hundred and 22 cirrhotic patients were included. Cirrhosis was defined according to clinical, histological, ultrasonographic or elastographic criteria. The majority of patients were male (62%) and the median age was 59 years (23–80). Patients were infected with GT1a (20%), 1b (67%) or 4 (10%). The median transient elastographic measurement was 21.8 KPa (P25 16.6; P75 33.3); the MELD score was 8(5–26) and the majority of patients (73.5%) were Child-Pugh A at baseline. Up to 58.5% of patients had previously failed to antiviral therapies; importantly 17% of them had already received a PI-based regimen. Baseline median ALT was 69(5– 513) and viral load (HCV-RNA) was 6.06 log10 IU/mL (1.28–8.29). The majority of patients (78%) were treated for 12 weeks and 62% of the cohort received RBV. Fourteen patients are still on treatment; 8 patients had to prematurely discontinue therapy (1 due to an allergic reaction, 1 committed suicide, 1 had hepatocellular carcinoma progression, 2 patients presented liver decompensation and in 3 cases was unknown). At the end of treatment (EOT), all patients had undetectable serum HCV-RNA. The rates of sustained virological response (SVR) 4 and 12 weeks after therapy were 95.5% (485/505) and 88.5% (415/469), respectively. SVR rate was similar among patients, regardless of the use or not of RBV. There were 54 (8.7%) reported virological failures. Safety profile will be reported. Conclusions: The combination of SOF/SMV (with or without RBV) is very effective in cirrhotic patients infected with GT1 and 4 in Spain. The high prevalence of G1b infection may explain the higher efficacy compared with other real-life cohorts.
ARISING OF SIMEPREVIR DRUG-RESISTANCE Q80K IN HEPATITIS C VIRUS SUBTYPE 1A CLADE 2 ISOLATES

<table>
<thead>
<tr>
<th>Company</th>
<th>Johnson &amp; Johnson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Simeprevir</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>THU-243</td>
</tr>
</tbody>
</table>

**Abstract Body**

Background and Aims: Hepatitis C virus subtype 1a (HCV-1a) isolates can be separated into two distinct clades (1 and 2). Of note, the simeprevir inhibitor drug-resistance Q80K was only detected in HCV-1a clade 1 sequences but not in clade 2. Several informative sites for this clade distinction are located proximal to or within codons associated with resistance to NS3 protease inhibitors. The aims of this study were to identify if any clade informative sites are in direct contact with the Q80 residue and simulate the implications that could hinder the emergence of Q80K in clade 2 sequences. Methods: The web server RING was used to generate a twodimensional network of non-covalent, hydrogen bonds and van der Waals interactions on the tri-dimensional NS3-4A protein (PDB 2O8M). Subsequently, based on the protein information of the HCV-1a clade 2 sequence (EU155345), manual mutations were performed on PDB 2O8M structure using the program PyMOL to obtain wild-type (Q80) and mutant (K80) proteins. Molecular dynamics (MD) simulations were performed with GROMOS96 53a6 force field employing the GROMACS program package. Long-range nonbonded interactions were treated by particle-mesh Ewald summation. The Berendsen scheme was used to maintain temperature (300K) and pressure by weak coupling to an external bath. Results: We identified and selected a subset of 9 residues involved in direct contact with Q80 amino acid in the Cytoscape 3.2 program, including one residue from the protease catalytic triad (Asp 81) and one clade informative residue (N174). As only HCV-1a clade 2 sequences present the amino acid glycine (G) at position 174, we simulated the implications that hinder the emergence of Q80K on HCV-1a clade 2 proteins. During simulation, larger root mean square deviation (RMSD) indicates an increase on protein structural flexibility. The backbone RMSD of the wild-type protease observed over time showed larger final values, amplitudes and a shorter equilibration time than backbone RMSD of the mutant protease. In addition, K80 displayed a higher distance from the catalytic residue D81, which could impair NS3 proteolytic capacity and make it difficult the emergence in clade 2 viral populations. Conclusions: These findings could partially explain the lack of detection of simeprevir drug-resistance Q80K in HCV-1a clade 2 dominant viral populations. However, given the nature of replicative RNA viruses, additional mutations may occur in HCV genome and support the emergence of K80 variants in clade 2 isolates.
Background and Aims: This study aimed to evaluate the prevalence and impact of baseline (BL) resistance-associated variants (RAVs) on ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) or simeprevir/ sofosbuvir (SMV/SOF) ± RBV regimens in patients with genotype (GT) 1 HCV infection in HCV-TARGET, a multi-centre, prospective, observational cohort study. Methods: A subset of patients enrolled in HCV-TARGET were consented to serum collection prior to initiating HCV therapy administered according to local standard of care. HCV resistance testing was performed on samples collected before May 12, 2015 using Monogram Biosciences assays (population sequence derived from Illumina MiSeq data with a 10% variant reporting threshold). LDV, SOF and SMV susceptibility was interpreted using Monogram’s rule-based algorithm. Results: BL resistance testing was performed for 486 patients treated with LDV/SOF (n = 209), LDV/SOF + RBV (n = 31), SMV/SOF (n = 186) or SMV/SOF + RBV (n = 60). Demographics included 63% male, 13% Black, 76% GT1a, 52% cirrhosis, 18% with liver transplant, and 55% with prior HCV therapy. The overall prevalence of SMV, LDV and SOF RAVs was 41% (196/480), 24% (116/484) and 2.7% (13/480), respectively. The prevalence of SMV, LDV and SOF RAVs in treatment-naïve (TN) patients (221/486) was 39%, 23%, and 3.2%, respectively, compared to 42%, 25%, and 2.3% in treatment-experienced (TE) patients (265/486). The prevalence of SMV, LDV and SOF RAVs in non-cirrhotic patients (233/486) was 37%, 24% and 2.2%, respectively, compared to 44%, 24% and 3.2% in cirrhotic patients (253/486). To date (403/486 with SVR12 data), 91.3% (368/403) of patients achieved SVR12, and 8.7% (35/403) developed relapse, had no response or had virologic breakthrough. In the LDV/SOF ± RBV cohort (n = 168), 85% (17/20) with LDV or SOF RAVs achieved SVR12, whereas 95% (141/148) without LDV and SOF RAVs achieved SVR12. For the SMV/SOF ± RBV cohort (n = 227), 88% (85/97) with SMV RAVs and 90% (135/150) without SMV RAVs achieved SVR12. Multivariate analysis incorporating RAVs associated with SVR12 for the 486 patient cohort will be presented. Conclusions: SMV, LDV and SOF RAVs at BL for GT1 patients treated with LDV/SOF ± RBV or SMV/SOF ± RBV suggests that the prevalence was generally comparable between TN and TE patients, and between cirrhotic and non-cirrhotic patients.
**C-EDGE HEAD-TO-HEAD: EFFICACY AND SAFETY OF ELBASVIR AND GRAZOPREVIR COMPARED WITH SOFOSBUVIR/PEGYLATED INTERFERON/RIBAVIRIN: A PHASE 3 RANDOMIZED CONTROLLED TRIAL**

<table>
<thead>
<tr>
<th>Company</th>
<th>Merck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Zepatier (Grazoprevir / Elbasvir)</td>
</tr>
</tbody>
</table>

**Abstract Body**
IN A 5-DAY MONOTHERAPY TRIAL, MK-8408 DEMONSTRATES POTENT ANTIVIRAL ACTIVITY AND IMPROVED RESISTANCE PROFILE IN HCV PATIENTS WITH GENOTYPES 1, 2, AND 3 INFECTIONS

Company  Merck
Drug  MK-8408
Abstract Number  THU-222

Abstract Body  Background and Aims: MK-8408 is a potent NS5A inhibitor with activity across all major HCV genotypes (GTs, 1–6) in vitro. MK-8408 retains activity against resistance-associated polymorphisms in NS5A and clinically-relevant resistance-associated variants (RAVs) selected by approved NS5A inhibitors. Preclinical and clinical pharmacokinetics supported a once-daily oral administration of MK-8408. MK-8408 was evaluated in a 5-day monotherapy doseranging study in patients chronically infected with HCV GTs 1, 2 or 3. Given the potential for RAVs to impact the activity of NS5A inhibitors, we investigated the presence and impact of baseline NS5A RAVs in these patients. Methods: MK-8408 was administered for 5 days at a dose of 60 mg once-daily in patients (N = 3/arm) infected with GT1, GT2 or GT3; doses of 10, 30 and 120 mg were also evaluated in GT3 patients. Prior to the first dose, patient plasma samples were genotyped and aliquots retained to investigate presence of baseline NS5A RAVs. Plasma samples were obtained at pre-defined time-points post-dose for evaluation of viral load and presence of RAVs by population sequencing. Clonal sequencing was conducted on a subset of samples to investigate RAV linkage. Results: MK-8408 demonstrated potent antiviral activity in patients infected with HCV GT1, GT2 or GT3. At the 60 mg dose a mean maximal HCV viral load reduction (log10) of 3.86 ± 0.21, 3.62 ± 0.41 and 3.35 ± 0.9 was observed in GT1, GT2 and GT3 patients, respectively. No baseline NS5A RAVs were detected in GT1 patients. There was no difference in antiviral activity in GT2 patients with viruses bearing the common resistance-associated M31 polymorphism as compared to those with L31. GT3 patients who were infected with viruses bearing NS5A RAVs (A30K, S62F/L, and Y93H) at baseline showed no reduction of antiviral activity. However, in 3 GT3 patients, a combination of 2 or more linked NS5A RAVs that included Y93H at baseline reduced MK-8408 clinical activity consistent with >1000-fold potency reduction in replicons bearing these combinations of NS5A amino acid substitutions. Conclusions: A 60 mg dose of MK-8408, a potent next-generation NS5A inhibitor, administered orally once-daily for 5 days, reduced HCV RNA by >3 log10 in HCV GT1, GT2 or GT3 patients. The presence of single baseline NS5A polymorphisms did not impact MK-8408 clinical activity in HCV GT1, GT2 or GT3 patients demonstrating an improved resistance profile compared to approved inhibitors in this class.
C-EDGE CO-STAR: FAVORABLE IMPACT OF ELBASVIR AND GRAZOPREVIR ON HEALTH-RELATED QUALITY OF LIFE IN TREATMENT-NAÏVE HCV-INFECTED PERSONS WHO INJECT DRUGS RECEIVING OPIOID AGONIST THERAPY

Company  Merck
Drug Zepatier (Grazoprevir / Elbasvir)

Abstract Number THU-225

Abstract Body

Background and Aims: A Phase 3, double-blind, placebo-control, randomized trial of an oral fixed dose combination of elbasvir (EBR, an HCV NS5A inhibitor) 50 mg / grazoprevir (GZR, an HCV NS3/4A protease inhibitor) 100 mg once daily for 12 weeks was conducted among treatment-naïve HCV GT1-4, or 6-infected patients who inject drugs receiving opioid agonist therapy (OAT). EBR/GZR was demonstrated to be highly effective (SVR12: 95.5% (95% CI: 91.5%, 97.9%)) and generally well-tolerated, with a similar safety profile to placebo. The aim of this study was to evaluate whether HCV treatment with EBR/GZR altered the health-related quality of life (HRQOL) profile in patients on OAT. Methods: HRQOL was assessed using the SF-36V2® Acute Health Survey. Patients completed the SF-36V2® at baseline, treatment week 4 (TW4), TW12, follow-up week 4 (FW4), and FW12 (EBR/GZR arm only). 301 patients were randomized and received ≥1 dose of study drug (EBR/GZR: n = 201, Placebo: n = 100). The aim of this study was to estimate the mean changes in health domains’, mental component summary (MCS) and physical component summary (PCS) scores from baseline to TW12 by treatment group. Results: Overall, 98% of patients completed a baseline and at least one post-baseline HRQOL assessment. Mean HRQOL scores were similar between treatment groups at baseline. Between baseline and TW12, patients receiving EBR/GZR had more favorable changes in HRQOL compared to placebo [Figure]. The EBR/GZR group had mean improvements from baseline scores, with mean change scores >0, in Physical Functioning, Bodily Pain, General Health, Vitality, Mental Health, PCS and MCS. Mean declines ((<0) were noted for all the health domains’ and summary scores for the placebo group. Conclusions: Treatment with EBR/GZR had a favorable impact on the HRQOL profile compared to placebo in patients with chronic HCV GT1, 4 or 6 infections receiving OAT.
HIGH EFFICACY OF AN 8-WEEK 3-DRUG REGIMEN OF GRAZOPREVIR/MK-8408/MK-3682 IN HCV GENOTYPE 1, 2 AND 3-INFECTED PATIENTS: SVR24 DATA FROM THE PHASE 2 C-CREST 1 AND 2 STUDIES

Company | Merck
---|---
Drug | Grazoprevir / MK-8408 / MK-3682
Abstract Number | SAT-139

**Abstract Body**

Background and Aims: Hepatitis C virus (HCV) regimens that contain 3 potent direct-acting antiviral agents, each targeting different steps in the viral life cycle, may prevent the emergence of resistance increase antiviral efficacy, and permit a shorter duration of therapy. The aim of Part A of the C-CREST 1 and 2 studies was to evaluate the safety and efficacy of once-daily 3-drug regimens for 8 weeks, including grazoprevir (GZR), an NS3/4A protease inhibitor; elbasvir (EBR) or MK-8408, NS5A inhibitors; and MK-3682, an NS5B polymerase inhibitor. Methods: These were randomized, open-label, dose-ranging Phase 2 studies in treatment-naïve, noncirrhotic patients with HCV genotype (GT)1, 2 (C-CREST-1) or 3 (C-CREST-2) infection. Patients received EBR 50 mg/MK-3682 300 mg or 450 mg/GZR 100 mg or GZR 100 mg/MK-8408 60 mg/MK-3682 300 mg or 450 mg. All patients were treated for 8 weeks and followed for 24 weeks after completion of therapy. The primary efficacy endpoint was sustained virologic response at follow-up week (FUW) 12 (SVR12); the secondary efficacy outcome was SVR24. Analysis of HCV resistance-associated variants (RAVs) was performed at baseline in all patients, and at failure and during followup in those with virologic failure. Results: 240 patients were enrolled (GT1a, n = 46; GT1b, n = 47; GT2, n = 61; GT3, n = 86). All patients completed the full 8 weeks of dosing and have FUW12 data. Across treatment arms, 98% (45/46) of GT1a and 98% (46/47) GT1b patients achieved SVR12. The GZR/MK-8408/MK-3682 (450 mg) regimen achieved SVR12 in 94% (15/16) of GT2 patients and 91% (20/22) of GT3 patients. To date, there have been no relapses between FUW12 and FUW24. Based on population sequencing, high rates of SVR were maintained in patients with NS5A RAVs at baseline. Data for the NS3, NS5A and NS5B loci by next-generation sequencing will be presented. Treatments were generally safe and well tolerated, with no discontinuations due to adverse events and no cardiac or renal signals. Conclusions: An 8-week regimen of GZR/MK-8408/MK-3682 (450 mg) was highly effective, with SVR12 >90% in treatment-naïve, noncirrhotic patients with HCV GT1, 2 or 3 infection, including those with NS5A RAVs at baseline. SVR24 has remained high, demonstrating sustained response following completion of therapy. Based on the results of Part A, GZR/MK-8408/MK-3682 (450 mg) is being evaluated further in Part B of C-CREST 1 and 2, which includes HCV-infected patients with cirrhosis, prior treatment failure, and HIV/HCV co-infection.
COST-EFFECTIVENESS OF ELBASVIR (EBR, MK-8742)/GRAZOPREVIR (GZR, MK-5172) USE IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS (HCV) GENOTYPE 1 INFECTION AND CHRONIC KIDNEY DISEASE (CKD) IN THE UNITED STATES

Company: Merck
Drug: Zepatier (Grazoprevir / Elbasvir)
Abstract Number: SAT-141

Abstract Body:
Background and Aims: HCV infection is an important cause of morbidity, end-stage liver disease (ESLD) mortality from decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), cardiovascular and end-stage renal disease (ESRD) mortality, and costs in CKD patients in the United States. We evaluated the cost-effectiveness of EBR/GZR in CKD patients compared with no treatment (NoTX) and pegylated interferon plus ribavirin (peg-IFN/RBV). Methods: A computer-based model of the natural history of chronic HCV genotype 1 infection, CKD, and liver disease was developed to project lifetime cumulative incidence of DC, HCC, liver-transplant (LT), kidney transplant (KT), ESLD mortality, ESRD mortality, and associated lifetime costs and quality-adjusted life years (QALY). Efficacy of EBR/GZR of 0.99 (0.95–1.00) was obtained from C-SURFER, a phase 2/3 double-blind, placebo-control trial in HCV genotype 1-infected patients with CKD4/5. Based on a meta-analysis, we assumed an efficacy of 0.60 (0.47–0.71) for peg-IFN/RBV. Data on baseline characteristics of the simulated patients were obtained from NHANES. Other model's inputs were estimated from published studies. Cost of treatment with EBR/GZR was assumed to be similar to that of recently launched directly-acting agents. We conducted Monte Carlo simulations to estimate mean and 95% uncertainty intervals (UI) of outcomes. Results: Compared with NoTx, use of EBR/GZR was projected to reduce the lifetime cumulative incidence of HCC from an average of 19.96% (UI: 7.25–37.23) to an average of 0.89% (UI: 0.04–3.63) (Table 1). EBR/GZR-based regimens reduced lifetime cumulative incidence of DC from 8.80% (UI: 3.06–16.97) when peg-IFN/RBV was used to 3.19% (UI: 0.16–11.35). Use of EBR/GZR reduced ESLD mortality to 0.23% (UI: 0.00–0.99) from 10.60% (UI: 3.71–21.31) with peg-IFN/RBV and 26.56% (UI: 14.23–41.08) with NoTx. Compared with NoTx, use of EBR/GZR lowered ESRD mortality from 12.70% (UI: 8.41–18.02) to 11.88% (UI: 10.34–13.46). EBR/GZR-based regimens resulted in higher average remaining QALYs and higher costs, and were cost-effective at a threshold of $100,000/QALY in 99.8% of the simulations. Conclusions: Use of EBR/GZR was projected to substantially reduce the incidence of liver- and CKD-related complications and mortality in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. In addition, EBR/GZR is cost-effective in the United States at commonly cited thresholds.
C-EDGE IBLD: EFFICACY AND SAFETY OF ELBASVIR/GRAZOPREVIR (EBR/GZR) IN SUBJECTS WITH CHRONIC HEPATITIS C VIRUS INFECTION AND INHERITED BLOOD DISORDERS

Company: Merck
Drug: Zepatier (Grazoprevir / Elbasvir)

Abstract Number: SAT-128

Abstract Body: Background and Aims: Complications from chronic hepatitis C virus (HCV) infection remain a major cause of morbidity and mortality among individuals with inherited blood disorders (IBLD), including those with haemophilia (HEM), beta thalassemia (BTHAL), von Willebrand disease (VWD) and sickle cell anaemia (SCA). Inability to tolerate ribavirin and frequent comorbidities have limited HCV treatment options in these patients. The efficacy and safety of a once-daily, fixed-dose combination of EBR 50 mg (NS5A inhibitor) and GZR 100 mg (NS3/4A protease inhibitor) has been demonstrated in a broad population of HCV-infected patients and supported evaluation in the IBLD population. Methods: C-EDGE-IBLD is a double-blind, placebo-controlled study that randomized treatment-naïve (TN) and peg-IFN/RBV treatment experienced (TE) HCV genotype (GT)1, 4 or 6-infected patients in a 2:1 ratio to either an immediate treatment group (ITG; 12 weeks of EBR/GZR) or deferred treatment group (DTG; 12 weeks of placebo, followed by EBR/GZR). Randomization was stratified according to cirrhosis status and IBLD group, defined as 1) HEM (A or B) or VWD, 2) BTHAL and 3) SCA. The primary endpoints for this study are proportion of patients in the ITG who achieved an SVR12 (HCV RNA 3× baseline and >100 U/L) in each arm. SVR12 results will be presented. Conclusions: Preliminary data indicate that EBR/GZR is well tolerated and effective in patients with HCV GT1, 4 or 6 with and without cirrhosis with IBLD.
C-SWIFT RETREATMENT FINAL RESULTS: HIGHLY SUCCESSFUL RETREATMENT OF GT1-INFECTED PATIENTS WITH 12 WEEKS OF ELBASVIR/GRAZOPREVIR PLUS SOFOSBUVIR AND RIBAVIRIN AFTER FAILURE OF SHORT-DURATION ALL-ORAL THERAPY

Company: Merck
Drug: Zepatier (Grazoprevir / Elbasvir)

Abstract Number: SAT-148

Abstract Body: Background and Aims: Therapies to retreat patients who have failed prior all-oral, direct-acting antiviral therapies have not been defined. The purpose of this study was to assess a retreatment regimen for subjects who had failed therapy with elbasvir/grazoprevir (EBR/GZR, an NS5A inhibitor + potent NS3/4A protease inhibitor fixed-dose combination) + sofosbuvir (SOF).

Methods: Genotype 1-infected patients who relapsed after therapy with EBR/GZR + SOF for 4, 6 or 8 weeks were offered retreatment with 12 weeks of EBR/GZR + SOF + ribavirin (RBV). The primary endpoint was the proportion of patients achieving hepatitis C virus RNA < 15 IU/mL 12 weeks after end of treatment (SVR12). Population sequencing was used to detect resistance-associated variants (RAVs) in NS3, NS5A and NS5B. Results: Twenty-five of 29 eligible patients were enrolled: 88% (22/25) with G1a infection; 20% (5/25) with cirrhosis; baseline viral load mean 6.6 log10 IU/mL (range: 4.3–7.4 log10 IU/mL). At baseline of retreatment, 80% (20/25) patients had NS5A RAVs, 52% (13/25) had an NS3 RAV and 0/25 had an NS5B RAV. NS5A variants at the following positions occurred in 16–32% of the retreatment population, M28, Q30, L31, H58 and Y93. Nine subjects had both an NS5A and NS3 RAV at baseline. Twenty-three of 25 subjects completed therapy. Two patients were lost to follow-up; one after treatment day 3 and one after treatment week 4, at which time viral load was 363 IU/mL and target not detected, respectively. SVR12 was achieved in 100% of the 23 patients who completed therapy. One patient discontinued RBV only due to pruritus. Rash, fatigue and nausea were the most frequent adverse events occurring in 8% of patients. Conclusions: 100% SVR12 was achieved with a 12-week regimen of EBR/GZR + SOF + RBV regardless of cirrhosis and high prevalence of RAVs (including two class RAVs). Final SVR24 results will be presented.
Background and Aims: The fixed-dose combination of elbasvir 50 mg, an NS5A inhibitor and grazoprevir 100 mg, an NS3/4 protease inhibitor (EBR/GZR), is a highly effective and well-tolerated all-oral, once-daily regimen in diverse populations of HCV GT1, 4, or 6-infected patients, including PWID on OAT. However, data on HCV reinfection rates after successful HCV treatment are limited, particularly in the interferon-free treatment era. Methods: The double-blind, placebo-controlled CO-STAR study evaluated the efficacy of EBR/GZR for 12 weeks in treatment-naïve HCV GT1/4/6-infected patients ± cirrhosis ± HIV receiving OAT. Patients were randomized 2:1 to an immediate treatment group (ITG) or a deferred treatment group. HCV reinfection was evaluated among ITG patients with undetectable HCV RNA at end of treatment (EOT). In patients with viremia recurrence following EOT, population sequencing and phylogenetic analysis of the NS3 and NS5A regions were performed on baseline and post-treatment samples to distinguish relapse from reinfection. Results: 301 patients were randomized, with 201 in the ITG (mean age 47 yrs; 76% male; 15% black; 76% GT1a; 20% cirrhotic, 8% HIV+). Baseline OAT included methadone (81%) and buprenorphine (19%), and 62% had detectable illicit drugs on urine drug screen. A total of 197/200 patients had undetectable HCV RNA at EOT. Post-treatment viremia was detected in 14 patients, with 7 virological relapses, and 7 probable HCV reinfections; 5 through follow-up week (FW)12 and an additional 2 at FW24 (GT1a to 6a, GT1a to 1a, GT1a to GT3a, GT6a to GT1b, GT6a to 6a, GT1a to 1a, GT1b to 1b). Two subjects previously identified as reinfections had subsequent clearance of HCV RNA at FW24. An estimate of reinfection incidence from EOT through FW12 is 10.6 (95%CI: 3.42, 24.6) per 100 person years. Follow-up analysis, including next generation sequencing of baseline/post-treatment viremic samples to determine if any probable reinfection cases were due to relapse of non-dominant baseline variants rather than reinfection, will be presented. The CO-STAR population will be followed for 3 years post-FW24 for ongoing evaluation of reinfection. Conclusions: Several HCV reinfection cases were detected among PWID on OAT following successful EBR/GZR therapy. Further followup is required to determine the natural course of HCV reinfection in the setting of interferon-free HCV treatment, and the impact of viral persistence following reinfection on long-term response rates in this population.
Background and Aims: Safe, efficacious and convenient antiviral regimens without interferon or ribavirin are being developed for chronic HCV infection. The C-EDGE TN study (P060) investigated the safety and efficacy of EBR (NS5A inhibitor) and GZR (NS3/4A protease inhibitor) in TN patients (pts) with GT1, 4 or 6 infection. Methods: An international, randomized, blinded, placebo-controlled, parallel-group trial of an oral fixed-dose combination of EBR 50 mg/ GZR 100 mg once daily for 12 weeks in TN pts with HCV GT1, 4 or 6 infection, with or without cirrhosis. Exclusion criteria were decompensated liver disease, HCC, HIV or HBV co-infection, platelets <50 × 10^3/μL or albumin <3.0 g/dL. Pts were assigned in a 3:1 ratio to receive immediate or deferred therapy after stratification by GT and fibrosis stage assessed by biopsy or noninvasive means. The primary efficacy endpoint was SVR12 in the immediate EBR/GZR arm (HCV RNA levels <15 IU/mL, 12 weeks after the end of treatment). SVR24 was a secondary endpoint. Results: Overall, 421 pts were randomized and received ≥1 dose of study drug: 194 (46%) were women; 157 (37%) were non-white; 382 (91%) had GT1, 26 (6%) had GT4, and 13 (3%) had GT6 infections. 92 (22%) pts had cirrhosis (biopsy-proven, n = 26 [28%]; median platelets [IQR] 123.5 × 10^3/μL [49.0–298.0]; median albumin [IQR] 4.1 g/dL [3.0–5.2]). Two patients in the deferred group did not receive active drug and were excluded from the efficacy analysis: all other pts have reached follow-up wk (FUW)24. SVR24 was achieved by 93.6% (392/ 419) of pts in the combined immediate and deferred groups. Virologic failure occurred in 21 (5%) pts (relapse, n = 18 [17 relapsed before/at FUW12 and 1 at FUW24]; virologic breakthrough, n = 3); 5 patients discontinued due to administrative reasons (death n = 2 [incarcerated hiatal hernia and cardiac arrhythmia, both on active treatment and considered unrelated to study drug], withdrawal by patient, n = 1; lost-to-follow-up, n = 2); and 1 patient discontinued due to a drugrelated AE (palpitations/anxiety on treatment day 4). Serious AEs occurred in 10 (3%) and 4 (4%) pts in the active and placebo groups. Next-generation sequencing data of resistance associated polymorphisms will be presented. Conclusions: A 12-week regimen of EBR/GZR was efficacious and well tolerated in TN pts with GT1 or 4 infection, including those with compensated cirrhosis. SVR24 has remained high, demonstrating sustained response following completion of therapy.
### Abstract Body

**RG-101 IN COMBINATION WITH 4 WEEKS OF ORAL DIRECT ACTING ANTIVIRAL THERAPY ACHIEVES HIGH VIROLOGIC RESPONSE RATES IN TREATMENT NAÏVE GENOTYPE 1 AND 4 CHRONIC HEPATITIS C PATIENTS: INTERIM RESULTS FROM A RANDOMISED, MULTI-CENTER, PHASE 2 STUDY**

<table>
<thead>
<tr>
<th>Company</th>
<th>Regulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>RG-101</td>
</tr>
</tbody>
</table>
## SEQUENCE ANALYSIS FOR RESISTANCE MONITORING FOLLOWING A SINGLE DOSE OF RG-101, AN ANTI-MIR TARGETING MICRORNA-122, IN CHRONIC HEPATITIS C PATIENTS

<table>
<thead>
<tr>
<th>Company</th>
<th>Regulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>RG-101</td>
</tr>
<tr>
<td>Abstract Number</td>
<td>THU-232</td>
</tr>
</tbody>
</table>

**Abstract Body**

Background and Aims: MicroRNA-122 (miR-122) plays a crucial role in the hepatitis C virus (HCV) life cycle. A single dose of RG-101, an oligonucleotide against miR-122, resulted in a decline in HCV RNA levels in chronic hepatitis C (CHC) patients. The aim of this study was to assess if nucleotide changes in the 5′ UTR of the HCV genome appeared in patients with viral rebound following RG-101 dosing. Methods: 32 CHC patients with genotype 1 (n = 16), 3 (n = 10) or 4 (n = 6) infection were included in a phase 1 study. Patients received a single injection of 2 or 4 mg/kg RG-101 (n = 28) or placebo (n = 4). All patients were followed for 8 weeks after randomization. Patients were followed from 8 up to 28 weeks after dosing, and follow-up ended if patients experienced a viral rebound (>1 log increase in HCV RNA from nadir). 5′ RACE and population-based sequencing of the HCV RNA 5′ UTR was done at baseline, and at time of viral rebound (if HCV RNA was >20,000 IU/mL). Deep sequencing was performed on baseline and select rebound samples. Sequences were compared with reference sequences and those from baseline samples to characterize HCV variants associated with viral rebound following RG-101 administration. Results: At baseline, none of the patients had a mutation in the first 250 nucleotides of the 5′ UTR, including the binding sites of miR-122, compared to reference sequence. In 11 patients who were dosed with RG-101 and experienced a viral rebound up to 28 weeks of study, a matched sample (at baseline and viral rebound) with a positive PCR signal following 5′RACE was available for analysis. 5/11 patients, infected with HCV genotype 1, had a C3U nucleotide change at time of viral rebound (weeks 8 to 16). In 2/11 patients, infected with HCV genotype 3 or 4, HCV variants containing C2G and C3U mutations and G1A and U4A polymorphisms were observed at time of viral rebound (week 8 and 12). In 4/11 patients (HCV genotype 1 or 3) with viral rebound after ≥16 weeks of follow-up, no nucleotide changes in the 5′ UTR were observed. Good agreement was seen between population and deep sequence analysis. Conclusions: HCV variants emerging 16 weeks after RG-101 administration.
Background and Aims: RG-101 is a GalNAc-conjugated antisense oligonucleotide inhibitor of the liver-expressed host cell factor microRNA-122 (miR-122), which has been shown to be required for replication of the hepatitis C virus (HCV). In preclinical studies, RG-101 dose dependently reduced viral load in genotype (GT) 1a and 3a HCV infected human liver chimeric mice. In a Phase 1 clinical trial, a single administration of RG-101 produced mean viral load reductions of 4.8 log (4 mg/kg) and 4.1 log (2 mg/kg) in patients infected with either HCV GT 1, 3, or 4 at day 29. To support additional clinical activities, we evaluated the in vitro antiviral activity of RG-101 against all HCV GTs, against HCV replicons resistant to NS3, NS5A and NS5B inhibitors, and in combination with direct acting antiviral (DAA) drugs. Methods: In vitro antiviral activity of RG-101 alone or in combination with other anti-HCV agents was performed in the GT 1b HCV replicon system. Other antiviral studies were performed using recombinant HCV strains that contained the 5’ UTR from HCV GTs 1 to 6, or HCV GT1b replicons constructed to contain DAA-resistance associated mutations. All studies with RG-101 were performed without the use of a transfection agent. Results: RG-101 demonstrated robust antiviral activity against HCV GT1b with mean EC50 and EC90 values of 0.23 μM and 9.0 μM, respectively. No cytotoxicity of RG-101 was observed up to the highest concentration tested (320 μM) indicating a favorable in vitro therapeutic index of >821. RG-101 also demonstrated antiviral activity against all HCV GTs tested (HCV GT 1a, 1b, 2a, 3a, 4a, 5a, or 6a). Combination studies of RG-101 with non-nucleoside and nucleoside inhibitors of NS5B (dasabuvir, sofosbuvir), NS5A (daclatasvir, ledipasvir, ombitasvir), or NS3 (simeprevir) indicated additive interactions. In addition, RG-101 demonstrated broad antiviral activity when tested against HCV replicons resistant to NS3, NS5A and NS5B inhibitors with less than 2-fold reductions in activity when compared to a wild-type HCV replicon. Conclusions: RG-101 has demonstrated robust in vitro antiviral activity against all HCV GTs, against HCV replicons resistant to NS3, NS5A and NS5B inhibitors, and in combination with other DAA drugs with little to no cytotoxicity. This data set supports the continued clinical development of RG-101 in HCV infected individuals.
**Abstract Body**

Background and Aims: In patients with chronic hepatitis C (CHC), natural killer (NK) cells express an altered phenotype. This phenotype has been shown to normalize after successful DAA treatment. Here we analysed the changes in the phenotype of NK cells in CHC patients who received a single dose of the anti-miRNA122 oligonucleotide RG-101. Methods: 32 Patients with CHC who participated in a phase 1 proof of concept study received a single subcutaneous injection with RG-101. Fourteen patients received 2 mg/kg, 14 patients 4 mg/kg, and 2 patients in each group received placebo. Peripheral blood mononuclear cells were collected at baseline, Day 15 and Day 57 (Week 8). Phenotypic analyses on NK cells were performed in a first subset of 19 patients (2 mg/kg: n = 10, 4 mg/kg: n = 9) by flowcytometry. HCV RNA levels were measured using Roche COBAS AmpliPrep/COBAS Taqman HCV v2.0 assay, with a reported LLOQ of 15 IU/mL. Results: After dosing with RG-101, HCV RNA declined in all patients (mean decline at Day 15: 3.27 log10 IU/mL). Furthermore in 12/19 patients, HCV RNA levels were below the limit of quantification (BLOQ) at Day 57. While the proportion of CD56dim NK cells increased during follow-up, the proportion of CD56bright cells was significantly lower at Day 57 after injection as compared to baseline (median 5.7 and 8.8 % of total NK cells respectively, p = 0.007). At Day 57, the expression of TRAIL, an important ligand for the induction of apoptosis, on CD56bright NK cells had decreased significantly as compared to baseline (14.6–7.6% of CD56bright NK cells, p < 0.0001). No differences were observed in baseline TRAIL expression between patients with and without HCV RNA BLOQ at day 57 (p = 0.16). Activating receptor (NKp30 and NKp46) expression and the expression of CD38, a marker for immunologic activity, decreased during follow-up. Conclusions: In patients with CHC, a single dose of RG-101 leads to a reduction in HCV RNA in all patients. Furthermore, NK cells shift towards a less activated phenotype, similar to what has been observed in CHC patients with viral load decline upon DAA treatment.
Disclosure section

The information and opinions in Morgan Stanley Research were prepared by Morgan Stanley & Co. LLC, and/or Morgan Stanley C.T.V.M. S.A., and/or Morgan Stanley Mexico, Casa de Bolsa, S.A. de C.V., and/or Morgan Stanley Canada Limited. As used in this disclosure section, "Morgan Stanley" includes Morgan Stanley & Co. LLC, Morgan Stanley C.T.V.M. S.A., Morgan Stanley Mexico, Casa de Bolsa, S.A. de C.V., Morgan Stanley Canada Limited and their affiliates as necessary.

For important disclosures, stock price charts and equity rating histories regarding companies that are subject of this report, please see the Morgan Stanley Research Disclosure Website at www.morganstanley.com/research/disclosures, or contact your investment representative or Morgan Stanley Research at 1505 Broadway, (Attention: Research Management), New York, NY, 10036 USA.

For valuation methodology and risks associated with any price targets reflected in this research report, please contact the Client Support Team as follows: US/Canada +1 800 303-2495; Hong Kong +852 2849-6999; Latin America +1 718 574-5444 (US), +1 212-742-8199; Singapore +65 6334-6880; Sydney +61 (2) 9770-1535; Tokyo +81 (3) 6363-8000. Alternatively you may contact your investment representative or Morgan Stanley Research at 1505 Broadway, (Attention: Research Management), New York, NY, 10036 USA.

Analyst Certification
The following analysts hereby certify that their views about the companies and their securities discussed in this report are accurately expressed and that they have not received direct or indirect compensation in exchange for expressing specific recommendations or views in this report:
Matthew Harrison.

Unless otherwise stated, the individuals listed on the cover page of this report are research analysts.

Global Research Conflict Management Policy
Morgan Stanley Research has been published in accordance with our conflict management policy, which is available at:

Important US Regulatory Disclosures on Subject Companies
As of February 29, 2016, Morgan Stanley beneficially owned 1% or more of a class of common equity securities of the following companies covered in Morgan Stanley Research:

Within the last 12 months, Morgan Stanley has received or managed a public offering or an investment banking services from the following companies:

Within the last 12 months, Morgan Stanley has received compensation for investment banking services from:

Within the last 12 months, Morgan Stanley has received compensation for investment banking services from:

Within the last 12 months, Morgan Stanley has received compensation for investment banking services from:

Within the last 12 months, Morgan Stanley has received compensation for investment banking services from:

The equity research analysts or strategists principally responsible for the preparation of Morgan Stanley Research have received compensation based upon various factors, including quality of research, investor client feedback, stock picking, competitive factors, firm revenues and overall investment banking revenue.

Disclosure section
Disclosure section (continued)

Morgan Stanley and its affiliates do business that relates to companies/instruments covered in Morgan Stanley Research, including market making, providing liquidity, fund management, commercial banking, extension of credit, investment services and investment banking. Morgan Stanley sells to and buys from customers the securities/instruments of companies covered in Morgan Stanley Research on a principal basis. Morgan Stanley may have a position in the debt of the Company or instruments discussed in this report. Certain disclosures listed above are also for compliance with applicable regulations in non-US jurisdictions.

**STOCK RATINGS**

Morgan Stanley uses a relative rating system using terms such as Overweight, Equal-weight, Not-Rated or Underweight (see definitions below). Morgan Stanley does not assign ratings of Buy, Hold or Sell to the stocks we cover. Overweight, Equal-weight, Not-Rated and Underweight are not the equivalent of buy, hold and sell. Investors should carefully read the definitions of all ratings used in Morgan Stanley Research. In addition, since Morgan Stanley Research contains more complete information concerning the analyst's views, investors should carefully read Morgan Stanley Research, in its entirety, and not infer the contents from the rating alone. In any case, ratings (or research) should not be used or relied upon as investment advice. An investor's decision to buy or sell a stock should depend on individual circumstances (such as the investor's existing holdings) and other considerations.

**Global Stock Ratings Distribution**

(as of February 29, 2016)

For disclosure purposes only (in accordance with NASD and NYSE requirements), we include the category headings of Buy, Hold, and Sell alongside our ratings of Overweight, Equal-weight, Not-Rated and Underweight. Morgan Stanley does not assign ratings of Buy, Hold or Sell to the stocks we cover. Overweight, Equal-weight, Not-Rated and Underweight are not the equivalent of buy, hold, and sell but represent recommended relative weightings (see definitions below). To satisfy regulatory requirements, we correspond Overweight, our most positive stock rating, with a buy recommendation; we correspond Equal-weight and Not-Rated to hold and Underweight to sell recommendations, respectively.

<table>
<thead>
<tr>
<th>STOCK RATING CATEGORY</th>
<th>COVERAGE UNIVERSE COUNT</th>
<th>% OF TOTAL</th>
<th>INVESTMENT BANKING CLIENTS (IBC) COUNT</th>
<th>% OF TOTAL</th>
<th>% OF RATING CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight/Buy</td>
<td>1216</td>
<td>36%</td>
<td>320</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>Equal-weight/Hold</td>
<td>1399</td>
<td>42%</td>
<td>320</td>
<td>44%</td>
<td>23%</td>
</tr>
<tr>
<td>Not-Rated/Hold</td>
<td>69</td>
<td>2%</td>
<td>3</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Underweight/Sell</td>
<td>671</td>
<td>20%</td>
<td>89</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>3,355</strong></td>
<td></td>
<td><strong>732</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data include common stock and ADRs currently assigned ratings. Investment Banking Clients are companies from whom Morgan Stanley received investment banking compensation in the last 12 months.

**Analyst Stock Ratings**

Overweight (O). The stock's total return is expected to exceed the average total return of the analyst's industry (or industry team's) coverage universe, on a risk-adjusted basis, over the next 12-18 months.

Equal-weight (E). The stock's total return is expected to be in line with the average total return of the analyst's industry (or industry team's) coverage universe, on a risk-adjusted basis, over the next 12-18 months.

Not-Rated (NR). Currently the analyst does not have adequate conviction about the stock's total return relative to the average total return of the analyst's industry (or industry team's) coverage universe, on a risk-adjusted basis, over the next 12-18 months.

Underweight (U). The stock's total return is expected to be below the average total return of the analyst's industry (or industry team's) coverage universe, on a risk-adjusted basis, over the next 12-18 months.

Unless otherwise specified, the time frame for price targets included in Morgan Stanley Research is 12 to 18 months.

**Analyst Industry Views**

Attractive (A). The analyst expects the performance of his or her industry coverage universe over the next 12-18 months to be attractive vs. the relevant broad market benchmark, as indicated below.

In-Line (I): The analyst expects the performance of his or her industry coverage universe over the next 12-18 months to be in line with the relevant broad market benchmark, as indicated below.

Cautious (C): The analyst views the performance of his or her industry coverage universe over the next 12-18 months with caution vs. the relevant broad market benchmark, as indicated below.

Benchmarks for each region are as follow: North America - S&P 500; Latin America - relevant MSCI country index or MSCI Latin America Index; Europe - MSCI Europe; Japan - Topix; Asia - relevant MSCI country index or MSCI sub-regional index or MSCI AC Asia Pacific ex Japan Index.

**Stock Price, Price Target and Rating History (See Rating Definitions)**
Important Disclosures for Morgan Stanley Smith Barney LLC Customers

Important disclosures regarding the relationship between the companies that are the subject of Morgan Stanley Research and Morgan Stanley Smith Barney LLC or Morgan Stanley or any of their affiliates, are available on the Morgan Stanley Wealth Management disclosure website at www.morganstanley.com/online/researchdisclosures. For Morgan Stanley specific disclosures, you may refer to www.morganstanley.com/researchdisclosures.

Each Morgan Stanley Equity Research report is reviewed and approved on behalf of Morgan Stanley Smith Barney LLC. This review and approval is conducted by the same person who reviews the Equity Research report on behalf of Morgan Stanley. This could create a conflict of interest.

Other Important Disclosures

Morgan Stanley & Co. International PLC and its affiliates have a significant financial interest in the debt securities of Amgen Inc., Biogen Inc, Celgene Corp, Gilead Sciences Inc., Gilead Sciences Inc., and Regeneron Pharmaceuticals Inc.

Morgan Stanley is not acting as a municipal advisor and the opinions or views contained herein are not intended to be, and do not constitute, advice within the meaning of Section 975 of the Dodd-Frank Wall Street Reform and Consumer Protection Act.

Morgan Stanley produces an equity research product called a “Tactical Idea.” Views contained in a “Tactical idea” on a particular stock may be contrary to the recommendations or views expressed in research on the same stock. This may be the result of differing time horizons, methodologies, market events, or other factors. For all research available on a particular stock, please contact your sales representative or go to Matrix at http://www.morganstanley.com/matrix.

Morgan Stanley Research is provided to our clients through our proprietary research portal on Matrix and also distributed electronically by Morgan Stanley to clients. Certain, but not all, Morgan Stanley Research products are also made available to clients through third-party vendors or redistributed to clients through alternate electronic means as a convenience. For access to all available Morgan Stanley Research, please contact your sales representative or go to Matrix at http://www.morganstanley.com/matrix.

Any access and/or use of Morgan Stanley Research is subject to Morgan Stanley’s Terms of Use (http://www.morganstanley.com/terms.html). By accessing and/or using Morgan Stanley Research, you are indicating that you have read and agree to be bound by our Terms of Use (http://www.morganstanley.com/terms.html). In addition you consent to Morgan Stanley processing your personal data and using cookies in accordance with our Privacy Policy and our Global Cookies Policy (http://www.morganstanley.com/privacy_pledge.html), including for the purposes of setting your preferences and to collect readership data so that we can deliver better and more personalized service and products to you. To find out more information about how Morgan Stanley processes personal data, how we use cookies and how to reject cookies see our Privacy Policy and our Global Cookies Policy (http://www.morganstanley.com/privacy_pledge.html).

If you do not agree to our Terms of Use and/or if you do not wish to provide your consent to Morgan Stanley processing your personal data or using cookies please do not access our research.

Morgan Stanley Research does not provide individually tailored investment advice. Morgan Stanley Research has been prepared without regard to the circumstances and objectives of those who receive it. Morgan Stanley Research does not independently evaluate particular investments and strategies, and encourages investors to seek the advice of a financial adviser. The appropriateness of an investment or strategy will depend on an investor’s circumstances and objectives. The securities, instruments, or strategies discussed in Morgan Stanley Research may not be suitable for all investors, and certain investors may not be eligible to purchase or participate in some or all of them. Morgan Stanley Research is not an offer to buy or sell or the solicitation of an offer to buy or sell any security/instrument or to participate in any particular trading strategy. The value of and income from your investments may vary because of changes in interest rates, foreign exchange rates, default rates, prepayment rates, securities/instruments prices, market indexes, operational or financial conditions of companies or other factors. There may be time limitations on the exercise of options or other rights in securities/instruments transactions. Past performance is not necessarily a guide to future performance. Estimates of future performance are based on assumptions that may not be realized. If provided, and unless otherwise stated, the closing price on the cover page is that of the primary exchange for the subject company’s securities/instruments.

The fixed income research analysts, strategists or economists principally responsible for the preparation of Morgan Stanley Research have received compensation based upon various factors, including quality, accuracy and value of research, firm profitability or revenues (which include fixed income trading and capital markets profitability or revenues), client feedback and competitive factors. Fixed Income Research analysts’, strategists’ or economists’ compensation is not linked to investment banking or capital markets transactions performed by Morgan Stanley or the profitability or revenues of particular trading desks.

The “Important U.S. Regulatory Disclosures on Subject Companies” section in Morgan Stanley Research lists all companies mentioned where Morgan Stanley owns 1% or more of a class of common equity securities of the companies. For all other companies mentioned in Morgan Stanley Research, Morgan Stanley may have an investment of less than 1% in securities/instruments or derivatives of securities/instruments of companies and may trade them in ways different from those discussed in Morgan Stanley Research. Employees of Morgan Stanley not involved in the preparation of Morgan Stanley Research may have investments in securities/instruments or derivatives of securities/instruments of companies mentioned and may trade them in ways different from those discussed in Morgan Stanley Research. Derivatives may be issued by Morgan Stanley or associated persons.

With the exception of information regarding Morgan Stanley, Morgan Stanley Research is based on public information. Morgan Stanley makes every effort to use reliable, comprehensive information, but we make no representation that it is accurate or complete. We have no obligation to tell you when opinions or information in Morgan Stanley Research change apart from when we intend to discontinue equity research coverage of a subject company. Facts and views presented in Morgan Stanley Research have not been reviewed by, and may not reflect information known to, professionals in other Morgan Stanley business areas, including investment banking personnel.

Morgan Stanley Research personnel may participate in company events such as site visits and are generally prohibited from accepting payment by the company of associated expenses unless pre-approved by authorized members of Research management.

Morgan Stanley may make investment decisions that are inconsistent with the recommendations or views in this report.
Disclosure section (continued)

To our readers in Taiwan: Information on securities/instruments that trade in Taiwan is distributed by Morgan Stanley Taiwan Limited ("MSTL"). Such information is for your reference only. The reader should independently assess the investment risks and is solely responsible for their investment decisions. Morgan Stanley Research may not be distributed to the public media or quoted or used by the public media without the express written consent of Morgan Stanley. Information on securities/instruments that do not trade in Taiwan is for informational purposes only and is not to be construed as a recommendation or solicitation to trade in such securities/instruments. MSTL may not execute transactions for clients in these securities/instruments. To our readers in Hong Kong: Information is distributed in Hong Kong by and on behalf of, and is attributable to, Morgan Stanley Asia Limited as part of its regulated activities in Hong Kong. If you have any queries concerning Morgan Stanley Research, please contact our Hong Kong sales representatives.

Morgan Stanley Research is not incorporated under PRC law and the research in relation to this report is conducted outside the PRC. Morgan Stanley Research does not constitute an offer to sell or the solicitation of an offer to buy any securities in the PRC. PRC investors shall have the relevant qualifications to invest in such securities and shall be responsible for obtaining all relevant approvals, licenses, verifications and/or registrations from the relevant governmental authorities themselves.

Morgan Stanley Research is disseminated in Brazil by Morgan Stanley C.T.V.M. S.A.; in Mexico by Morgan Stanley México, Casa de Bolsa, S.A. de C.V which is regulated by Comision Nacional Bancaria y de Valores, Paseo de los Tamarindos 90, Torre 1, Col Bosques de las Lomas Floor 29, 05120 Mexico City; in Japan by Morgan Stanley MUFG Securities Co., Ltd. and, for Commodities related research reports only, Morgan Stanley Capital Group Japan Co., Ltd. in Hong Kong by Morgan Stanley Asia Limited (which accepts responsibility for its contents) and by Bank Morgan Stanley AG, Hong Kong Branch in Singapore by Morgan Stanley Asia (Singapore) Pte. (Registration number 1990002902) and/or Morgan Stanley Asia (Singapore) Securities Pte Ltd (Registration number 2000084544), regulated by the Monetary Authority of Singapore (which accepts legal responsibility for its contents and should be contacted with respect to any matters arising from, or in connection with, Morgan Stanley Research) and by Bank Morgan Stanley AG, Singapore Branch (Registration number T11FC20017) in Australia to " wholesale clients" within the meaning of the Australian Corporations Act by Morgan Stanley Australia Limited A.B.N. 67 003 734 576, holder of Australian financial services license No. 233742, which accepts responsibility for its contents; in Australia to "wholesale clients" and "retail clients" within the meaning of the Australian Corporations Act by Morgan Stanley Wealth Management Australia Pty Ltd (A.B.N. 19 009 145 555, holder of Australian financial services license No. 240013, which accepts responsibility for its contents; in Korea by Morgan Stanley & Co International plc, Seoul Branch; in India by Morgan Stanley India Company Private Limited, in Indonesia by PT Morgan Stanley Asia Indonesia; in Canada by Morgan Stanley Canada Limited, which has approved of and takes responsibility for its contents in Canada; in Germany by Morgan Stanley Bank AG, Frankfurt am Main and Morgan Stanley Private Wealth Management Limited, Niederlassung Deutschland, regulated by Bundesanstalt fuer Finanzdienstleistungsaufsicht (BaFin); in Spain by Morgan Stanley, S.V., S.A., a Morgan Stanley group company, which is supervised by the Spanish Securities Markets Commission (CNMV) and states that Morgan Stanley Research has been written and distributed in accordance with the rules of conduct applicable to financial research as established under Spanish regulations; in the US by Morgan Stanley & Co. LLC, which accepts responsibility for its contents, Morgan Stanley & Co. International plc, authorized by the Prudential Regulatory Authority and regulated by the Financial Conduct Authority and the Prudential Regulatory Authority, disseminates in the UK research that it has prepared, and approves solely for the purposes of section 21 of the Financial Services and Markets Act 2000, research which has been prepared by any of its affiliates. RMB Morgan Stanley (Proprietary) Limited is a member of the JSE Limited and regulated by the Financial Services Board in South Africa. RMB Morgan Stanley (Proprietary) Limited is a joint venture owned equally by Morgan Stanley International Holdings Inc. and RMB Investment Advisory (Proprietary) Limited, which is wholly owned by FirstRand Limited. The information in Morgan Stanley Research is being disseminated by Morgan Stanley Saudi Arabia, regulated by the Capital Market Authority in the Kingdom of Saudi Arabia, and is directed at Sophisticated investors only.

The information in Morgan Stanley Research is being communicated by Morgan Stanley & Co. International plc (DFC Branch), regulated by the Dubai Financial Services Authority (the DFSA), and is directed at Professional Clients only, as defined by the DFSA. The financial products or financial services to which this research relates will only be made available to a customer who we are satisfied meets the regulatory criteria to be a Professional Client. The information in Morgan Stanley Research is being communicated by Morgan Stanley & Co. International plc (QFC Branch), regulated by the Qatar Financial Centre Regulatory Authority (the QFCRA), and is directed at business customers and market counterparties only and is not intended for Retail Customers as defined by the QFCRA.

As required by the Capital Markets Board of Turkey, investment information, comments and recommendations stated here, are not within the scope of investment advisory activity. Investment advisory service is provided exclusively to persons based on their risk and income preferences by the authorized firms. Comments and recommendations stated here are general in nature. These opinions may not fit to your financial status, risk and return preferences. For this reason, to make an investment decision by relying solely to this information stated here may not bring about outcomes that fit your expectations. The trademarks and service marks contained in Morgan Stanley Research are the property of their respective owners. Third-party data providers make no warranties or representations relating to the accuracy, completeness, or timeliness of the data they provide and shall not have liability for any damages relating to such data. The Global Industry Classification Standard (GICS) was developed by and is the exclusive property of MSCI and S&P Morgan Stanley Research, or any portion thereof may not be reprinted, sold or redistributed without the written consent of Morgan Stanley.
## Disclosure section (continued)

### INDUSTRY COVERAGE: Biotechnology

<table>
<thead>
<tr>
<th>Company</th>
<th>Rating As Of</th>
<th>Price (3/28/2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Andrew S Berens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aileron Pharma Inc (XLRN.O)</td>
<td>O (09/13/2015)</td>
<td>$23.92</td>
</tr>
<tr>
<td>Alkira Therapeutics Inc (AKRA.O)</td>
<td>O (09/08/2015)</td>
<td>$8.68</td>
</tr>
<tr>
<td>Campra Inc (CEMP.O)</td>
<td>O (11/16/2015)</td>
<td>$6.22</td>
</tr>
<tr>
<td>GW Pharmaceuticals PLC (GWPH.O)</td>
<td>O (08/13/2015)</td>
<td>$76.99</td>
</tr>
<tr>
<td>Ingle Corp (INCO)</td>
<td>O (02/22/2016)</td>
<td>$69.45</td>
</tr>
<tr>
<td>Interspec Pharmaceuticals Inc (ICPT.O)</td>
<td>E (10/29/2016)</td>
<td>$124.58</td>
</tr>
<tr>
<td>Kera Biopharmaceuticals Inc (KERA.O)</td>
<td>E (10/05/2016)</td>
<td>$4.55</td>
</tr>
<tr>
<td>Ocular Therapeutix Inc (OCUL.O)</td>
<td>O (02/17/2016)</td>
<td>$8.68</td>
</tr>
<tr>
<td>Replisa Inc (RLSP.O)</td>
<td>U (09/13/2015)</td>
<td>$12.95</td>
</tr>
<tr>
<td>Rodwell Medical Inc (RMNLQ)</td>
<td>O (08/13/2015)</td>
<td>$6.45</td>
</tr>
<tr>
<td>Versartis, Inc. (VSAR.O)</td>
<td>E (08/13/2015)</td>
<td>$6.57</td>
</tr>
</tbody>
</table>

| **Matthew Harrison** |
| Aileron Pharmaceuticals (ALNO.O) | O (10/01/2015) | $132.90 |
| Amgen Inc. (AMGN.O) | O (10/14/2015) | $145.37 |
| Biogen Inc (BIOI.O) | O (02/26/2016) | $27.03 |
| Biogen Inc (BBI.O) | O (02/26/2014) | $251.76 |
| Bluebird Bio Inc (BLUE.O) | E (12/07/2015) | $39.78 |
| Celazyme Corp (CELZ.O) | E (03/26/2014) | $189.22 |
| Cityzenxci (CMX.O) | U (02/22/2016) | $4.71 |
| Danaher Technologies SA (DBVT.O) | E (08/15/2015) | $30.45 |
| Editas Medicine (EDIT.O) | E (02/22/2016) | $30.53 |
| Galapagos NV (GLPG.O) | O (06/01/2015) | $41.13 |
| Gilead Sciences Inc. (GILD.O) | E (10/01/2015) | $82.46 |
| Global Blood Therapeutics Inc (GBT.O) | O (09/08/2015) | $12.99 |
| ImmunoGen Inc. (IMGN.O) | U (08/21/2015) | $7.67 |
| Influry Pharmaceuticals Inc (IFLO) | O (06/21/2015) | $4.95 |
| Innovia Inc (INVAO) | E (08/14/2015) | $11.65 |
| Ironwood Pharmaceuticals, Inc. (IRWD.O) | E (08/14/2015) | $10.11 |
| Juno Therapeutics Inc (JUNO) | O (08/14/2015) | $38.01 |
| MacroGenics Inc (MGNX.O) | E (08/25/2015) | $15.97 |
| Ophthotech Corp (OPHT.O) | O (08/14/2015) | $4.01 |
| Portola Pharmaceuticals Inc (PTLA.O) | E (08/14/2015) | $19.01 |
| Regeneron Pharmaceuticals Inc. (REGN.O) | O (10/01/2015) | $363.85 |
| Regeneron Inc (RGNX) | O (09/12/2015) | $96.62 |
| Syndax Pharmaceuticals Inc (SNDX.S) | O (03/26/2016) | $13.96 |
| Ultragenyx Pharmaceutical Inc (RARE.O) | E (07/27/2015) | $56.81 |
| Vertex Pharmaceuticals (VRTX.O) | O (10/01/2015) | $78.70 |

Stock Ratings are subject to change. Please see latest research for each company.
* Historical prices are not split adjusted.
# Disclosure section (continued)

<table>
<thead>
<tr>
<th>The Americas</th>
<th>Europe</th>
<th>Japan</th>
<th>Asia/Pacific</th>
</tr>
</thead>
<tbody>
<tr>
<td>1585 Broadway</td>
<td>20 Bank Street, Canary Wharf</td>
<td>4-20-3 Ebisu, Shibuya-ku</td>
<td>1 Austin Road West</td>
</tr>
<tr>
<td>New York, NY 10036-8293</td>
<td>London E14 4AD</td>
<td>Tokyo 150-6008</td>
<td>Kowloon</td>
</tr>
<tr>
<td>United States</td>
<td>United Kingdom</td>
<td>Japan</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>+1 212 761 4000</td>
<td>+44 (0)20 7425 8000</td>
<td>+81 (0) 3 5424 5000</td>
<td>+852 2848 5200</td>
</tr>
</tbody>
</table>