Poster 1058

# Daclatasvir Plus Sofosbuvir With or Without Ribavirin for the Treatment of Chronic HCV in Patients Coinfected With HIV: Interim Results of a Multicenter European Compassionate Use Program

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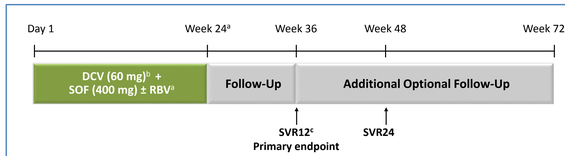
## BACKGROUND

- HCV-related liver disease is a leading cause of morbidity and mortality among HIV/HCV coinfected patients[1]
- Patients with HIV/HCV coinfection have increased risk of accelerated liver disease progression to cirrhosis and hepatic decompensation[1]
- Interferon-free regimens that can be co-administered with antiretroviral (ARV) therapy safely and with minimal drug-drug interactions are needed
- The pangenotypic, all-oral, RBV-free 12-week regimen of DCV and SOF was well tolerated and achieved 97% SVR rates in HIV/HCV coinfected patients receiving a wide range of ARVs in clinical trials (ALLY-2 study)[2]
- An extensive early access program provided access to DCV before market authorization to ≈ 7000 patients in urgent need of treatment
- Here we report interim results on the combination DCV plus SOF, with or without RBV in HIV/HCV coinfected patients enrolled in a European compassionate use program (CUP; AI444-237)[3]

RBV, ribavirin; DCV, daclatasvir (NS5A inhibitor); SOF, sofosbuvir (NS5B inhibitor)

## EUROPEAN DCV COMPASSIONATE USE PROGRAM

**Primary objective:** To provide access to DCV to patients with life-threatening chronic HCV infection who have no other treatment options




[a] Addition of RBV and shorter duration of treatment at the discretion of the physician

[b] Dose adjusted for concomitant ARVs: DCV 30 mg in combination with boosted protease inhibitors (PI); DCV 90 mg in combination with non-nucleoside reverse transcriptase inhibitors (NNRTI) except rilpivirine (RPV); No dose adjustment required in combination with integrase inhibitors (INI).

[c] HCV RNA < LLOQ, TD or TND at post-treatment Week 12 (next value carried backward approach)

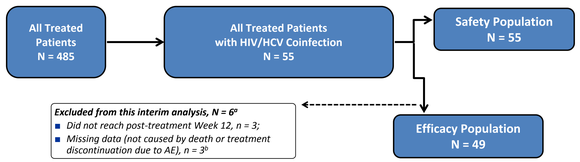
**Inclusion criteria**

- Age ≥ 18 years with no treatment options
- High risk of hepatic decompensation or death within 12 months if left untreated
  - Or urgent need of viral clearance (extrahepatic manifestations/comorbidities)

**Exclusion criteria**

- Creatinine clearance ≤ 30 mL/min
- Pregnancy or not using contraception

## STATISTICAL METHODS
### Interim Analysis




- **Primary Efficacy Analysis (mITT):**
  - SVR12: HCV RNA < LLOQ, TD or TND at post treatment Week 12[c]
  - Patients with missing data who died, discontinued treatment due to AEs, or had virological breakthrough / relapse before post-treatment Week 12 were classified as failures
- **Safety Analysis:**
  - Clinical (AE, serious AE, AE leading to discontinuation and death) and laboratory abnormalities

[a]All excluded patients had HCV RNA < LLOQ TD or TND at EOT (Week 24) or at the last available assessment (on-treatment Week 12).
[b] Includes 1 patient (DCV + SOF) with post-treatment Week 12 visit outside the predefined visit window (± 2 weeks); HCV RNA < LLOD TND at actual post-treatment Week 12 visit.
[c] Next value carried backward approach.

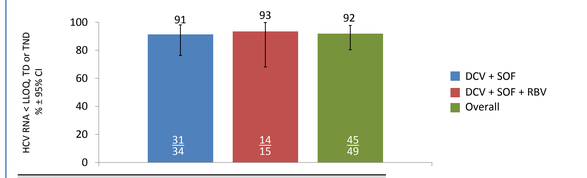
## RESULTS

**Table 1. Baseline Demographic and Disease Characteristics**

| Parameter | DCV + SOF N = 39 | DCV + SOF + RBV N = 16 | All Patients N = 55 |
|---|---|---|---|
| Age, median (range), years | 52.0 (37–67) | 50.5 (31–60) | 52.0 (31–67) |
| Male, n (%) | 30 (77) | 15 (94) | 45 (82) |
| White race, n (%) | 36 (92) | 16 (100) | 52 (95) |
| HCV genotype, n (%) | | | |
| 1a | 20 (51) | 6 (37.5) | 26 (47) |
| 1b | 6 (15) | 2 (12.5) | 8 (15) |
| 3 | 9 (23) | 6 (37.5) | 15 (27) |
| 4 | 3 (8) | 0 | 3 (5) |
| Mixed or unknown | 1 (3) | 2 (12.5) | 3 (5) |
| HCV RNA, median (range) $\log_{10}$ IU/mL[a,b] | 5.9 (1.1–6.7) | 6.1 (1.4–7.1) | 6 (1.1–7.1) |
| HCV RNA ≥ 2,000,000 IU/mL, n (%)[a,b] | 7 (18) | 5 (31) | 12 (22) |
| Cirrhosis, n (%)[c,d] | 38 (97) | 14 (88) | 52 (95) |
| Child-Pugh class, n (%)[e,f] | | | |
| A | 19 (50) | 6 (43) | 25 (48) |
| B | 16 (42) | 7 (50) | 23 (44) |
| C | 2 (5) | 1 (7) | 3 (5) |
| MELD score, median (range) | 10 (5–18) | 11 (7–28) | 10.5 (5–28) |
| Albumin, median (range) mg/L[g] | 35.9 (25–51) | 35.9 (25–50) | 35.9 (25–51) |
| Platelets, median (range) × $10^9$/L[h] | 86 (24–306) | 101 (31–178) | 89 (24–306) |
| Prior HCV therapy, n (%) | 23 (59) | 8 (50) | 31 (56) |
| HBV coinfection, n (%) | 3 (8) | 0 | 3 (5) |
| HIV RNA ≤ 50 copies/mL, n/N (%)[i] | 22/23 (96) | 7/9 (78) | 29/32 (91) |
| CD4 cell count category, n (%)[i] | N = 22 | N = 7 | N = 29 |
| < 200 /mm³ | 3 (14) | 1 (14.5) | 4 (14) |
| 200– < 350 /mm³ | 11 (50) | 2 (28.5) | 13 (45) |
| 350– < 500 /mm³ | 1 (4) | 2 (28.5) | 3 (10) |
| ≥ 500 /mm³ | 7 (32) | 2 (28.5) | 9 (31) |
| Antiretroviral regimens[j] | | | |
| Ritonavir-boosted PI (PI/r) – based, n (%)[j] | 15 (38) | 9 (56) | 24 (44) |
| Atazanavir | 3 | 2 | 5 |
| Darunavir | 8 | 4 | 12 |
| Lopinavir | 3 | 3 | 6 |
| Fosamprenavir | 1 | 0 | 1 |
| NNRTI-based, n (%) | 5 (13) | 4 (25) | 9 (16) |
| Efavirenz | 3 | 3 | 6 |
| Nevirapine | 1 | 0 | 1 |
| Rilpivirine | 1 | 1 | 2 |
| Integrase inhibitor (INI) – based, n (%) | 17 (44) | 3 (19) | 20 (36) |
| Raltegravir | 14 | 2 | 16 |
| Dolutegravir | 3 | 1 | 4 |
| Other (unboosted PI), n (%) | 2 (5) | 0 | 2 (4) |

[a] Excludes 3 patients with missing data; [b] HCV RNA assayed using the standard methods available at each site; [c] Diagnosed by liver biopsy (Metavir >F3, Ishak >4, or the equivalent), n = 3; FibroScan (>14.6 kPa), n = 40; or FIB-4 score (>3.25), n = 9; [d] 3 patients (1 DCV + SOF, 2 DCV + SOF + RBV) had indeterminate cirrhosis status; [e] Percentages based on cirrhotic patients; [f] Excludes 1 patient (DCV+SOF) with missing data; [g] Excludes 11 patients with missing data; [h] Excludes 1 patient with missing data; [i] Percentages based on number of patients with available data (N)
[j] Patients who received PI/r, except 1 (LPV/r-based regimen) received DCV 30 mg at baseline (2 patients increased DCV dose to 60 mg at Week 12); DCV dose was adjusted to 90 mg in patients taken EFV or NVP; No dose adjustment (DCV 60 mg) in patients treated with INI, RPV or unboosted PI.

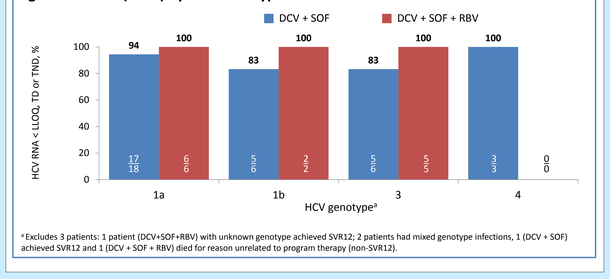
**Figure 2. Primary Efficacy Analysis – SVR12 (mITT)**




| Not Achieving SVR12 | 3 | 1 | 4 |
|---|---|---|---|
| Relapse[a] | 1 | 0 | 1 |
| Death[b] | 2 | 1 | 3 |

[a] Treatment-experienced (non-responder), cirrhotic patient (Child-Pugh B / MELD score 18) with HCV GT-1b infection (baseline HCV RNA, 5.31 $\log_{10}$ IU/mL) who received treatment with DCV (30 mg) + SOF for 24 weeks; ARV regimen: TDF/FTC + FPV/r.
[b] All deaths considered unrelated to program therapy.
Relapse defined as confirmed HCV RNA ≥ LLOQ during any post-treatment visit following HCV RNA < LLOQ, TD or TND, at end-of-treatment.

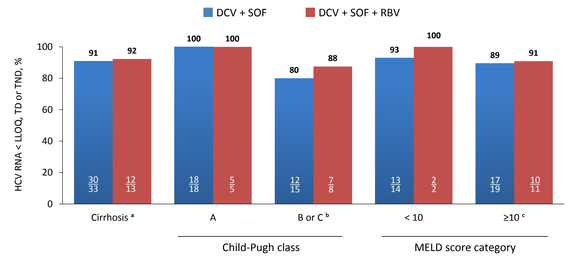
**Figure 3. SVR12 (mITT) by HCV Genotype**




[a] Excludes 3 patients: 1 patient (DCV+SOF+RBV) with unknown genotype achieved SVR12; 2 patients had mixed genotype infections, 1 (DCV + SOF) achieved SVR12 and 1 (DCV + SOF + RBV) died for reason unrelated to program therapy (non-SVR12).

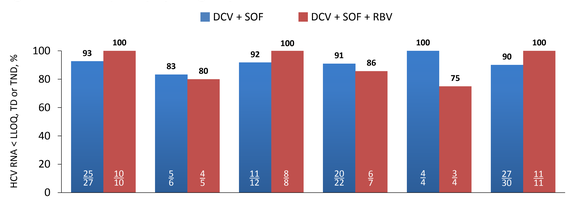
## RESULTS (cont)

**Figure 4. SVR12 (mITT) by Liver Disease Status**



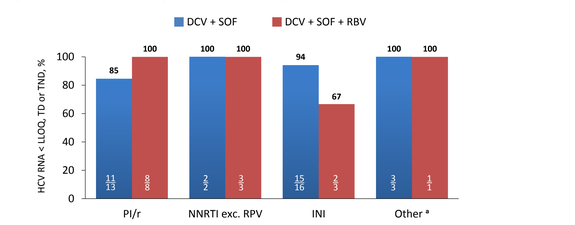

[a] Excludes 3 patients with indeterminate cirrhosis status; all achieved SVR12. No patients without cirrhosis were enrolled.
[b] 3 patients had Child-Pugh class C; 1 of 3 (DCV + SOF) achieved SVR12; 2 died for reasons unrelated to program therapy (non-SVR12).
[c] 4 patients had MELD scores 16–20 (2 of 4 achieved SVR12); 1 patient had a MELD score >25 (non-SVR12 due to death).

**Figure 5. SVR12 (mITT) by Subgroups**



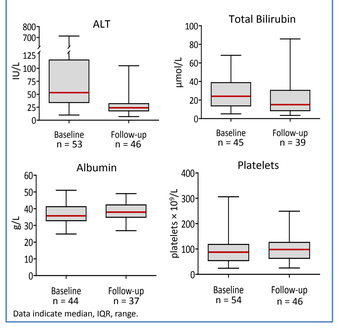

[a] Excludes 1 patient with unknown baseline HCV RNA level (achieved SVR12).
[b] Duration of therapy estimated based on time of exposure to treatment: 12-week arm includes 4 patients who received treatment < 12 weeks (3 achieved SVR12; 1 death); 24-week arm includes 1 patient who received treatment < 20 weeks (achieved SVR12).

**Figure 6. SVR12 (mITT) by Antiretroviral Regimen**



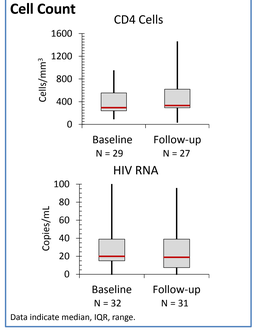

[a] Includes: RPV-based, n = 2 (1 DCV + SOF, 1 DCV + SOF+ RBV); unboosted PI (n = 2) (DCV + SOF); all 4 were treated with the DCV 60 mg dose. PI/r, boosted protease inhibitor regimen; NNRTI, non-nucleoside reverse transcriptase inhibitor regimen; INI, integrase inhibitor regimen.

**Figure 7. Changes in Liver Function From Baseline**




Data indicate median, IQR, range.

**Figure 8. Changes in HIV RNA/CD4 Cell Count**




Data indicate median, IQR, range.

## RESULTS (cont)

**Table 2. On-Treatment Safety Summary**

| Patients, n (%) | DCV + SOF N = 39 | DCV + SOF + RBV N = 16 | All Patients N = 55 |
|---|---|---|---|
| Total AEs, n (%) | 28 (72) | 11 (69) | 39 (71) |
| Serious AEs, n (%) | 9 (23) | 3 (19) | 12 (22) |
| Treatment-related serious AEs | 0 | 0 | 0 |
| AEs leading to discontinuation or death[a] | 5 (13) | 2 (13) | 7 (13) |
| Anemia | - | 1 (6) | 1 (2) |
| Arthralgia | 1 (3) | - | 1 (2) |
| Hepatocellular carcinoma | 1 (3) | - | 1 (2) |
| Pneumonia[b] | 1 (3) | - | 1 (2) |
| Psychotic disorder | 1 (3) | - | 1 (2) |
| Deaths[c] | 2 (5) | 1 (6) | 3 (5) |
| Multi-organ failure[b] | 1 (3) | - | 1 (2) |
| Alcohol consumption | 1 (3) | - | 1 (2) |
| Myocardial infarction | - | 1 (6) | 1 (2) |
| Most frequent AEs (≥ 5% of patients) | | | |
| Headache | 5 (13) | 1 (6) | 6 (11) |
| Fatigue | 2 (5) | 2 (13) | 4 (7) |
| Anemia | 4 (10) | 0 | 4 (7) |
| Diarrhea | 3 (8) | 1 (6) | 4 (7) |
| Nausea | 2 (5) | 2 (13) | 4 (7) |
| Vomiting | 1 (3) | 2 (13) | 3 (5) |
| Treatment-emergent grade 3 or 4 laboratory abnormalities, n (%) | | | |
| Hemoglobin < 90 g/L | 0 | 1 (6) | 1 (2) |
| ALT > 5 × ULN | 0 | 0 | 0 |
| AST > 5 × ULN | 0 | 0 | 0 |
| Total bilirubin > 2.5 × ULN[d] | 3 (9) | 3 (25) | 6 (13) |
| Creatinine > 1.9 × ULN | 0 | 0 | 0 |

[a] 1 event (arthralgia) considered possibly treatment-related; [b] More than 1 event reported in the same patient; [c] All deaths considered unrelated to program therapy; [d] 3 patients taking ATV-based regimens.

- No HIV virologic failure reported during the program period

## SUMMARY AND CONCLUSIONS

- In a real-world setting, treatment with DCV + SOF ± RBV achieved a high SVR12 rate (92%) in 49 patients with HIV/HCV coinfection, including 46 with compensated or decompensated cirrhosis
  - Similar SVR12 was observed in patients treated with or without RBV
  - Only 1 virologic failure (relapse, treated with DCV 30 mg)
- Similarly high SVR12 rates across wide range of concomitant antiretroviral regimens
  - Control of HIV disease indicators was maintained during HCV therapy
- Improvements in ALT and total bilirubin were observed between baseline and post-treatment Week 12
- DCV + SOF ± RBV was generally safe and well tolerated
  - No treatment-related serious AEs; few treatment-emergent grade 3 or 4 lab abnormalities
- These results indicate that DCV + SOF + RBV achieves high SVR12 rates and is well tolerated in patients with HIV/HCV coinfection, including patients with advanced liver disease

## REFERENCES

1. Graham CS, et al. *Clin Infect Dis* 2001;33:562–569.
2. Wyles DL, et al. *N Engl J Med* 2015;373:714–725.
3. EU CUP, AI444-237; ClinicalTrials.gov identifier NCT02097966.

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