GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use Post-Heart Transplant

This document is in response for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) for the treatment of HCV in heart transplant recipients.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Summary

Product Labeling[1]

SOF/VEL is not indicated for use in post-heart transplant.

Clinical Data on SOF/VEL Use Post-Heart Transplant

The DONATE HCV Trial was an open-label study that evaluated the safety and efficacy of 4 weeks of SOF/VEL in 35 participants who received heart or lung transplants from HCV+ donors. All participants achieved SVR12 and SVR24. No AEs were related to treatment.[2]

A prospective study evaluated the durability of SVR after heart, kidney, or liver transplantation, and all were aviremic throughout a median follow-up of 4 years. No safety findings were reported.[3]

A retrospective cases series evaluated efficacy, safety, and trends in renal function in HCV- patients who received SOF-based treatment after transplantation with HCV+ donor hearts. All patients achieved SVR12 and no significant changes in eGFR were noted 1 year post-transplant.[4]

Clinical Data on SOF/VEL Use Post-Heart Transplant

DONATE HCV: HCV- Recipients of HCV+ Donor Heart or Lungs

Study design and demographics[2]

A single-center, open-label pilot study was conducted to evaluate the safety and efficacy of heart or lung transplants from HCV+ donors to HCV- participants. The study was composed of participants who received an organ from a donor with active HCV infection (NAT+), regardless of HCV GT; starting on the day of transplant, participants received SOF/VEL for 4 weeks. The primary endpoint was combination of SVR12 and graft survival at post-

transplant Month 6, and serial HCV VL, Ab, and LFT monitoring was performed through SVR24 (secondary endpoint).

Results for 36 lung transplants and 8 heart transplants met the scientific objectives outlined in the protocol, so those results were provided. Of the 44 participants enrolled, 35 had ≥6 months of follow-up (including 7 heart transplant recipients), and 16 had ≥12 months of follow-up. Overall, the median (IQR) follow-up duration and donor HCV VL were 284 (171–385) days and 890,000 (276,000–4.63 million) IU/mL, respectively. HCV GTs included were GT 1 (61%), GT 2 (17%), GT 3 (17%), and indeterminate (5%).

Characteristics and outcomes of participants were compared with those from a cohort of 78 HCV- recipients of heart or lung transplants from HCV- donors from the same center and time period (53 lung and 24 heart transplants). Of these, 56 had ≥6 months of follow-up (including 12 heart transplant recipients), and 22 had ≥12 months of follow-up.

Table 1. Baseline Demographics and Characteristics of Heart Transplant Recipients With ≥6 Months of Follow-Up (Woolley et al)[2]

Recipient Demographics and Characteristics	NAT+ Donor (n=7)	HCV- Donor (n=12)
Age, median (range), y	51 (23–68)	52 (43–68)
Male, n (%)	6 (86)	6 (50)
White, n (%)	6 (86)	10 (83)
United Network for Organ Sharing waitlist status, 1A/1B/2, n	1/5/1[a]	12/0/0[a]
Length of time on waitlist, median (range), d	559 (90–2366)	183 (3–1596)

[a]*P*<0.05 for comparison between HCV NAT+ donors and HCV- donors.

Efficacy[2]

SVR12 and SVR24 were achieved by all 35 participants (100%) with ≥6 months of follow-up. Of the 9 participants with <6 months of follow-up, 5 achieved SVR4 and 4 had undetectable VL between Weeks 4 and 8. Nearly all (95%; 42/44) transplant recipients had a detectable HCV VL after transplant, and the median (IQR) initial VL was 1800 (800–6180) IU/mL. Twenty-seven of the 35 participants (77%) were HCV Ab+ at post-transplant Week 1, and 17 (49%) were HCV Ab+ at post-transplant Month 6.

Nearly all participants (94%; 15/16) with ≥12 months of follow-up had graft survival, and 1 recipient of a heart transplant died at post-transplant Month 8 (disseminated bacterial infection, deemed unrelated to treatment).

Table 2. Comparison of Outcomes Between HCV NAT+ and HCV- Donor Heart Transplant Recipients With ≥6 Months of Follow-Up (Woolley et al)[2]

Recipient and Donor Characteristics		NAT+ Donor (n=7)	HCV- Donor (n=12)	OR or Mean Difference[a] (95% CI)
Donor ischemic time, mean, min		269	236	33.64 (-20.5, 87.78)
Cardiopulmonary bypass time, mean, min		167	170	-3.7 (-44.61, 37.21)
Duration of hospital stay after transplantation, mean, d		49	72	-22.8 (-100.54, 54.94)
Duration of ICU stay, mean, d		38	36	2.12 (-77.28, 81.52)
Readmissions, median, n		1	2	-
LFTs ≥3 × ULN, n (%)	<30 d post-transplantation	3 (43)	8 (67)	2.53 (0.27, 27.33)
	≥30 d post-transplantation	0	1 (8)	NE (0.1, NE)
Stage 4 or 5 CKD at Month 6, n (%)		2 (29)	4 (33)	1.24 (0.12, 18.58)
Dialysis at Month 6, n (%)		1 (14)	2 (17)	1.19 (0.05, 82.4)
Respiratory failure at Month 6, n (%)		1 (14)	3 (25)	1.93 (0.12, 122.13)

Recipient and Donor Characteristics		NAT+ Donor (n=7)	HCV- Donor (n=12)	OR or Mean Difference[a] (95% CI)
Acute cellular rejection requiring treatment, n (%)		3 (43)	4 (33)	0.68 (0.07, 7.06)
Graft survival, n (%)	Month 1	7 (100)	11 (92)	0 (0, 66.79)
	Month 6	7 (100)	10 (83)	0 (0, 9.25)
Overall survival at Month 6		7 (100)	10 (83)	0 (0, 9.25)

Abbreviations: ICU=intensive care unit; NE=not estimable; OR=odds ratio; ULN=upper limit of normal.
[a]Categorical data are shown with unadjusted ORs and continuous data are shown with mean differences.

Safety

Safety data were only provided for HCV-mismatched transplant recipients, though study investigators noted that safety outcomes were similar between NAT+ and HCV- donor recipients.

Among HCV-mismatched transplant recipients, no AEs were deemed to be related to the study medication, and safety was not reported specifically for heart transplant recipients.[2] Overall, Grade 3 or 4 AEs were reported by 34 of 35 participants. Grade 3 or 4 AEs (n≥5) occurred within 30 days of transplantation: anemia, atrial fibrillation, hypotension, right ventricular dysfunction, and respiratory failure. The following Grade 3 or 4 AEs (n≥5) occurred ≥30 days after transplantation: rejection, renal insufficiency, pneumonia, and pleural effusion.[2,5]

Prospective Real-World Study: Durability of SVR in Transplant Recipients Treated With DAAs[3]

Study design and demographics

Participants who received heart (n=16), kidney (n=15), or liver (n=11) transplants and achieved SVR12 after DAA treatment and had ≥3 months of post-SVR12 follow-up were eligible for inclusion in this prospective, real-world study to determine the long-term durability of SVR. DAA treatment (for 8–12 weeks; ± ribavirin) was started in participants with chronic HCV and in those who had acute HCV infection within 2 weeks of transplantation with HCV+ organs. Baseline demographics were not reported according to the type of organ transplanted or the DAA used. Overall, 38 participants (90.5%) received SOF-based treatment, including 22 (52.4%) who received SOF/VEL.

Table 3. Baseline Demographics and Disease Characteristics of All Organ Transplant Recipients (Liu et al)[3]

Key Demographics and Characteristics	Overall (N=42)
Age, median (range), y	57 (12–79)
Male, n (%)	24 (57.1)
Type of organ transplanted, heart/kidney/liver, n (%)	16 (38.1)/15 (35.7)/11 (26.2)
Type of HCV infection, chronic/acute, n (%)	38 (90.5)/4 (9.5)
HCV RNA, median (range), $\log_{10}$ IU/mL	6.33 (1.43–7.71)
HCV GT, 1a/1b/2/3/6/3+6, n (%)	6 (14.3)/21 (50)/12 (28.6)/1 (2.4)/1 (2.4)/1 (2.4)
Stage of fibrosis,[a] 0–1/2/3/4, n (%)	22 (52.4)/11 (26.2)/5 (11.9)/4 (9.5)

[a]Assessed via transient elastography (Fibroscan®): Stage 0 to 1, ≤7 kPa; Stage 2, 7.1 to 9.4 kPa; Stage 3, 9.5 to 12.4 kPa; Stage 4, ≥12.5 kPa.

Efficacy and safety

Participants were followed for a median (IQR) of 4 (1–6) years (164.5 person-years of follow-up) after achieving SVR12. Three HCV- participants received HCV+ hearts and developed acute HCV; each received SOF/VEL for 12 weeks. and follow up ranged from 1 to 5 years. All participants achieved SVR24, and none had HCV viremia during follow-up. No safety findings were reported.

Retrospective Case Series in Heart Transplant Recipients[4]

Study design and demographics

A retrospective, single-center case series evaluated trends in renal function and the safety and efficacy of SOF-based DAA regimens in HCV- recipients of HCV+ donor (HCV Ab- or NAT+) hearts. Patients underwent heart transplantation (N=47; 1 patient had a history of successful pretransplant HCV treatment), and those who developed HCV infection were treated with LDV/SOF (HCV GT 1) for 12 weeks or SOF/VEL (HCV GT 3) for 12 to 24 weeks.

Five patients died during the first year post transplant, including 3 who died during the initial hospitalization due to primary graft dysfunction and multiorgan failure and 2 who died post discharge due to acute pulmonary embolism and multiorgan dysfunction. Of the remaining 42 patients, 9 did not develop HCV infection. Data from the remaining 33 patients were analyzed; SVR12 data were available for 23 patients (Cohort A), and 1 year of follow-up data were available for 18 patients (Cohort B). Ten patients were either still receiving DAA therapy or had not completed sufficient follow-up and were therefore not included in either cohort. In Cohorts A and B, 30% and 28% of patients received SOF/VEL, respectively.

Table 4. Baseline Demographics and Characteristics of Recipients With SVR12 Data (Zalawadiya et al)[4]

Key Recipient Demographics and Characteristics	Cohort A (n=23)	Cohort B (n=18)
Age, mean (SD), y	54 (11)	53 (12)
Male, %	83	89
Caucasian, %	70	67
Non-ischemic cardiomyopathy, %	52	61
Concomitant inotropes/LVAD/IABP, %	83/52/17	83/44/22
Previous heart transplant, %	9	17
Time on waiting list, mean (SD), d	320 (615)	329 (665)
Time on waiting list after entering study, mean (SD), d	43 (116)	30 (56)
Simultaneous heart-kidney transplant, %	0	6
Time to DAA initiation post-transplant, median (IQR), d	43 (37–74)	42 (37–74)

Abbreviations: IABP=intra-aortic balloon pump; LVAD=left ventricular assist device.

Efficacy and safety

Initiation of DAA therapy occurred at a median of 6 weeks post heart transplant. All patients achieved SVR12 and the majority (17/18) of patients with 1 year of follow-up data achieved SVR12.

All recipients with SVR12 data completed DAA treatment without interruption. The most common treatment-related AEs included fatigue (26%), headache (17%), and upset stomach (17%). Similar rates of AEs were reported between those with eGFR <60 mL/min/1.73 m^2 and those with eGFR ≥60 mL/min/1.73 m^2 (50% vs 39%; *P*=0.68).

Renal safety results

There were no significant differences in the median eGFR levels observed between time points and for each cohort. Approximately half of the patients in Cohort A had CKD Stage ≥3 at baseline, at DAA initiation, and at Week 12 (48%, 44%, and 52%, respectively). The proportion of patients with CKD Stage ≥4 increased from baseline (4%) to DAA initiation (9%) and at Week 12 (9%). At Week 12, 100% of patients (3/3) who began DAAs within 3 months of heart transplant had CKD Stage ≥3 compared with 45% (9/20) who began DAAs ≥3 months post transplant (*P*=0.217). Four patients (at DAA initiation: CKD Stage ≥3, n=1; CKD Stage <3, n=3) experienced worsening of renal function during treatment (based on ≥25% eGFR reduction from DAA initiation and completion) without improvement by Week 12. The VL of those 4 patients at DAA initiation was ≥25 million IU/mL and was significantly greater than the median VL observed the remaining 19 patients (9 million IU/mL; *P*=0.012). No patient required permanent hemodialysis or kidney transplant during the first year post transplant.

Table 5. eGFR Trends Over the Course of the Study (Zalawadiya et al)[4]

	eGFR, Median (IQR), mL/min/1.73 m^2					
	Baseline	**DAA Initiation**	**DAA Completion**	**SVR12**	**Month 6**	**Year 1**
Cohort A (n=23)	62 (51–84)	65 (44–85)	52 (41–81)	49 (37–82)	-	-
Cohort B (n=18)	65 (54–84)	-	-	-	75 (37–85)	56 (39–75)

Note: There were no significant differences in medians within each cohort.

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Woolley AE, Singh SK, Goldberg HJ, et al. Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. *N Engl J Med.* 2019;380(17):1606-1617. https://www.ncbi.nlm.nih.gov/pubmed/30946553
3. Liu CH, Chen YS, Tsai MK, et al. Long-term durability of sustained virologic response for hepatitis C virus infection in solid organ transplant recipients receiving direct-acting antivirals. *J Formos Med Assoc.* 2023;122(8):800-804.
4. Zalawadiya SK, Lindenfeld J, Shah A, et al. Trends in Renal Function Among Heart Transplant Recipients of Donor-Derived Hepatitis C Virus. *ASAIO J.* 2019. https://www.ncbi.nlm.nih.gov/pubmed/31425256
5. Woolley AE, Singh SK, Goldberg HJ, et al. Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients [Supplementary Appendix]. *N Engl J Med.* 2019;380(17):1606-1617. https://www.ncbi.nlm.nih.gov/pubmed/30946553

Abbreviations

Ab=antibody
AE=adverse event
CKD=chronic kidney disease
DAA=direct-acting antiviral
GT=genotype
LDV=ledipasvir
LFT=liver function test
LVAD=left ventricular assist device
NAT=nucleic acid testing
SOF=sofosbuvir
SVR=sustained virologic response
SVR4/12/24=sustained virologic response 4/12/24 weeks after end of treatment
VEL=velpatasvir
VL=viral load

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact privacy@gilead.com.