GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use Post Lung Transplant

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

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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 lung transplant recipients.

Clinical Data on SOF/VEL Use in Lung Transplant Recipients

SOF/VEL was administered for 4 weeks in a study of 35 HCV-negative participants who received heart or lung transplants from HCV-positive donors. All participants achieved SVR12 and SVR24, and no AEs or SAEs were related to SOF/VEL treatment.[2]

In a prospective Canadian study, 22 HCV-negative participants received lung transplants from HCV NAT-positive donors; 20 of those participants acquired HCV and received SOF/VEL treatment for 12 weeks. The SVR12 rate was 90% (18/20), and clinical outcomes were not significantly different between participants who received lungs from HCV-positive and HCV-negative donors. No SAEs were related to SOF/VEL treatment.[3]

In a case series of HCV-negative participants (N=5) who received HCV-positive donor lung transplants, 4 participants received LDV/SOF for 12 weeks (GT 1a, n=3; GT 1b, n=1), and 1 participant received SOF/VEL for 12 weeks (GT 2). SVR12 was 100% (5/5), and no AEs were attributable to HCV treatment.[4]

Clinical Data on SOF/VEL Use in Lung Transplant Recipients

DONATE HCV Trial: HCV-Negative Recipients of HCV-Positive 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 HCV-mismatched transplants in HCV-negative participants on the waitlist for heart or lung

transplants from HCV-positive donors between March 1, 2017, and July 31, 2018. Results were compared with results from a cohort of participants who received lung or heart transplants from HCV-negative donors during the same time period.

Study Arm A was composed of participants who received an organ from a donor with active HCV infection (NAT-positive), regardless of HCV GT; starting on the day of transplant, participants received SOF/VEL for 4 weeks. Study Arm B was composed of participants who received an organ from a donor with prior HCV infection (HCV Ab-positive/NAT-negative); participants received SOF/VEL for 6 weeks if viremia occurred.

Only the results for Study Arm A (36 lung transplants and 8 heart transplants) met the scientific objectives outlined in the protocol, so those results were provided. Thirty-five participants had ≥6 months of follow-up, and 16 participants had ≥12 months of follow-up.

Among the comparator cohort (HCV-negative donors), 53 lung transplants and 24 heart transplants were conducted during the study period. Fifty-six of these participants had ≥6 months of follow-up, and 22 participants had ≥12 months of follow-up.

Figure 1. DONATE HCV: Study Design–Study Arm A (Woolley et al)[2]

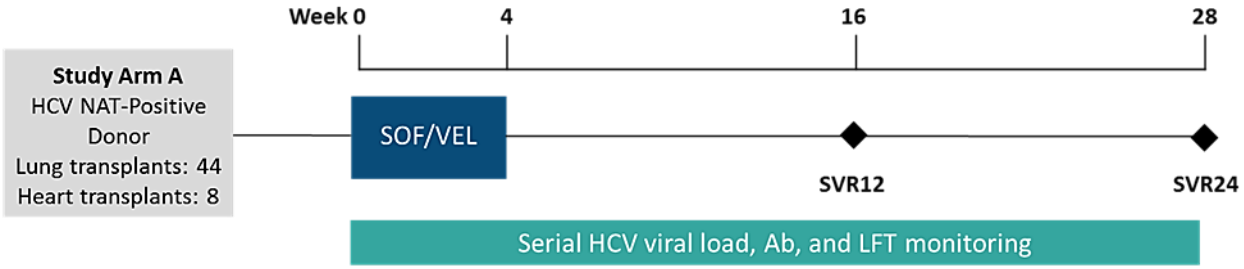

Table 1. DONATE HCV: Overall Baseline Demographics of HCV-Mismatched Transplants (Woolley et al)[2]

Overall Demographics and Characteristics	HCV-Mismatched Organ Transplants (N=44)
Follow-up duration, median (IQR), days	284 (171–385)
Donor HCV VL, median (IQR), IU/mL	890,000 (276,000–4.63 million)
HCV GT, 1/2/3/indeterminate, %	61/17/17/5

Table 2. DONATE HCV: Baseline Demographics and Characteristics of Lung Recipients and Donors[a] (Woolley et al)[2]

Recipient and Donor Demographics and Characteristics		Lung Transplants	
		HCV NAT-Positive Donor (n=28)	HCV-Negative Donor (n=44)
Recipient	Age, median (range), years	61 (41–71)	63 (28–71)
	Male, n (%)	11 (39)[b]	29 (66)[b]
	White, n (%)	26 (93)	40 (91)
	Lung allocation score, median	33.31[b]	38.16[b]
	UNOS waitlist status, 1A/1B/2, n	-	-
	Duration on waitlist, median (range), days	136 (17–2616)	79 (3–2521)

Recipient and Donor Demographics and Characteristics		Lung Transplants	
		HCV NAT-Positive Donor (n=28)	HCV-Negative Donor (n=44)
Donor	Age, median (range), years	32 (21–53)	33 (14–64)
	Increased-risk donor, n	100[b]	20[b]
	Illicit drug use within 6 months of death, n	71	50

Abbreviation: UNOS=United Network for Organ Sharing.
[a]HCV NAT-positive data are from the participants with ≥6 months of follow-up (n=35, including lung transplant recipients); HCV-negative data are from participants who received HCV-negative organs and had ≥6 months of follow-up (n=56, including lung transplant recipients).
[b]*P*<0.05, for comparison between HCV NAT-positive donors and HCV-negative donors by organ.

Efficacy

SVR12 and SVR24 were achieved by all participants (100%; 35/35) with ≥6 months of follow-up. Nearly all transplant recipients (95%; 42/44) had a detectable HCV VL after transplant, and the median (IQR) initial VL was 1800 (800–6180) IU/mL. By post-transplant/treatment Week 2, all recipients had an undetectable VL. Twenty-seven of the 35 participants (77%) had positive HCV Ab tests at post-transplant Week 1, and half (49%; 17/35) had positive HCV Ab tests at post-transplant Month 6.[2]

Nearly all of the 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).[2]

Comparison with HCV-negative donor-recipient transplants

Table 3. Comparison of Outcomes Between HCV-Positive and HCV-Negative Lung Donor Transplant Recipients (Woolley et al)[2]

Clinical Outcomes		Lung Transplants		Odds Ratio or Mean Difference (95% CI)
		HCV NAT-Positive Donor (n=7)	HCV-Negative Donor (n=12)	
Donor ischemic time, mean, minutes		327	281	46.65 (12.43–80.87)
Cardiopulmonary bypass time, mean, minutes		185	199	-14.84 (-37.81 to 8.13)
Grade 3 pulmonary graft dysfunction at 72 h, n (%)		0	3 (7)	NE (0.26–NE)
Hospital stay after transplantation, mean, days		14	21	-6.88 (-12.24 to -1.52)
Length of ICU stay, mean, days		6	10	-4.03 (-8.05 to -0.01)
Readmissions, median, n		2	2	-
LFTs ≥3 × ULN, n (%)	<30 days post transplantation	2 (7)	5 (11)	1.66 (0.25–18.62)
	≥30 days post transplantation	2 (7)	7 (16)	2.43 (0.42–25.83)
Stage 4 or 5 CKD at Month 6, n (%)		8 (29)	9 (20)	0.65 (0.19–2.26)
Dialysis at Month 6, n (%)		1 (4)	1 (2)	0.63 (0.01–51.1)
Respiratory failure at Month 6, n (%)		0	4 (9)	NE (0.43–NE)
ACR requiring treatment, n (%)		15 (54)	13 (30)	0.37 (0.12–1.09)
Graft survival, n (%)	Month 1	28 (100)	43 (98)	0 (0–61.23)
	Month 6	28 (100)	43 (98)	0 (0–61.23)
Overall survival at Month 6, n (%)		28 (100)	43 (98)	0 (0–61.23)

Abbreviations: ACR=acute cellular rejection; CKD=chronic kidney disease; NE=not estimable; ULN=upper limit of normal.

Safety

No AEs or SAEs were deemed to be related to the study medication. Ab-mediated rejection was observed in 1 participant (4%) who received a lung transplant from an HCV-positive donor and in 5 participants (15%) who received lung transplants from HCV-negative donors.[2]

Nearly all (34/35) of the HCV-mismatched transplant recipients had Grade 3 or 4 AEs, which resulted in 155 AEs. The following Grade 3 or 4 AEs (frequency ≥5) occurred within 30 days of transplantation: anemia, atrial fibrillation, hypotension, right ventricular dysfunction, and respiratory failure. The following Grade 3 or 4 AEs (frequency ≥5) occurred >30 days after transplantation: rejection, renal insufficiency, pneumonia, and pleural effusion.[2,5]

Prospective Canadian Study of HCV-Negative Recipients of HCV-Positive Donor Lung Transplants[3]

Study design and demographics

A prospective, single-center, open-label, non-randomized study assessed the clinical outcomes of HCV-negative participants who received lung transplants from HCV NAT-positive donors. Clinical outcomes were compared with those of participants who received lungs from HCV-negative donors. HCV RNA was assessed once daily for the first week after transplantation and then once weekly for 12 weeks or until start of treatment; all participants who became viremic received 12 weeks of SOF/VEL treatment. The primary outcomes were 6-month survival and the proportion of participants who were HCV negative. Secondary outcomes included the incidence of HCV transmission from donor to recipient and the time from transplantation to viremia.

Table 4. Baseline Demographics and Characteristics of Lung Recipients and Donors (Cypel et al)[3]

Recipient and Donor Demographics and Characteristics		Lung Transplants	
		HCV NAT-Positive Donor (n=22)	HCV-Negative Donor (n=187)
Recipient	Age, median (IQR), years	65 (60–68)	60 (47–67)
	Canadian waitlist status 2–3,[a] n (%)	11 (50)	125 (67)
	Positive crossmatch, n (%)	4 (18)	26 (14)
	Single lung, n (%)	11 (50)	30 (16)
	Duration on waitlist, median (IQR), days	17 (13–133)	42 (13–169)
Donor	Age, median (IQR), years	33 (29–37)	52 (30–65)
	HCV GT 1a/2/3, n (%)	14 (64)/3 (14)/ 5 (22)	N/A
	HCV RNA, median (IQR), $\log_{10}$ IU/mL	6.19 (5.91–6.73)	N/A
	Smoker, n (%)	20 (90)	88 (47)
	EVLP, n (%)	22 (100)	65 (35)

[a]Canadian waitlist status levels are as follows: Status 1 includes participants who are stable on a low concentration of oxygen; Status 2 includes participants who require high oxygen concentrations or have pulmonary hypertension or both; Status 3 includes participants with a rapid decline in lung function and are generally hospitalized or are in an ICU unit.

Efficacy

At 6 months after lung transplantation, 19 participants (86%) were alive and had undetectable HCV RNA. Twenty of the 22 participants (91%) who received lung transplants

from HCV NAT-positive donors acquired HCV infection with a median (IQR) time to viremia of 3 (2–5) days. The median (IQR) HCV VL at Day 7 was 3.08 (2.19–4.02) log_{10} IU/mL. All 20 participants who acquired HCV initiated SOF/VEL treatment at a median (IQR) of 21 (16.76–24.75) days after transplantation. All participants had undetectable HCV RNA at end of treatment, and 90% of participants (18/20) achieved SVR12. Two participants relapsed at 8 and 12 weeks after end of treatment; both achieved SVR12 after a 24-week course of SOV/VEL/VOX + RBV.

Comparison with HCV-negative donor-recipient transplants

Clinical outcomes were not significantly different between recipients of HCV-positive and HCV-negative donor lungs (Table 5).

Table 5. Comparison of Outcomes Between HCV-Positive and HCV-Negative Lung Donor Transplant Recipients (Cypel et al)[3]

Clinical Outcomes	Lung Transplants		% Difference (95% CI)
	HCV-Positive Recipient (n=22)	HCV-Negative Recipient (n=187)	
Length of stay in ICU, median (IQR), days	4.5 (2–14)	3.5 (2–7)	1 (-1 to 3)
Length of stay in hospital, median (IQR), days	31 (18.5–44)	22 (15–31)	9 (1–14)
Primary graft dysfunction Grade 3 at 72 hours, n (%)	3 (14)	11 (6)	8 (-3 to 30)
ECMO post transplant, n (%)	2 (9)	8 (4)	5 (-4 to 26)
Acute rejection A1 or higher per biopsy, n (%)	11 (50)	80 (43)	7 (-15 to 29)
Mortality at 90 days, n (%)	1 (4)	8 (4)	<1 (-6 to 20)
Survival at Month 6, n (%)	21 (95)	176 (94)	1 (-18.5 to 8)

Abbreviation: ECMO=extracorporeal membrane oxygenation.

Safety

No AEs or SAEs related to SOF/VEL treatment were observed. The most common Grade 3 or 4 AEs in participants who received lungs from HCV-positive donors included respiratory complications (n=5 [23%]) and infections (n=4 [18%]). The most common SAEs included pneumothorax, pneumonia, and fever (each, n=2 [9%]). Ten participants (45%) experienced SAEs that required hospital admission. One participant who did not acquire HCV infection died secondary to multiorgan failure related to *Pseudomonas* sepsis 31 days after transplantation.

Case Series of HCV-Negative Recipients of HCV-Positive Donor Lung Transplants[4]

Study design and demographics

A case series of HCV-negative participants who underwent double-lung transplants and received HCV-positive donor lungs at the University of Alberta Hospital between November 2016 and February 2017 was conducted to assess safety outcomes (N=5). Four of the 5 donors were ≤40 years of age; had known chronic, untreated HCV infection with detectable HCV RNA levels; and continued high-risk behaviors prior to death, such as IV drug usage, high-risk sexual contact, recent incarceration, and tattoos by non-licensed individuals. The fifth donor (aged 64 years) was also positive for HCV RNA at the time of transplant workup but had never been treated with antivirals.

All lung transplant recipients became viremic between post-transplant Days 1 and 16, and the highest VLs were observed in 2 participants whose donor lungs were placed on EVLP. Four participants received LDV/SOF (GT 1a, n=3; GT 1b, n=1), 1 participant received SOF/VEL (GT 2), and all received antiviral treatment for 12 weeks. The time to initiation of antivirals ranged from 24 to 94 days and was delayed due to the need for participants to be clinically stable and able to tolerate the entire course of oral antiviral therapies.

Results

All 5 participants achieved SVR12.

Table 6. Outcomes in HCV-Negative Recipients of HCV-Positive Donor Lungs (Abdelbasit et al)[4]

Recipient Characteristics and Outcomes	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5
Age, years/sex	65/Male	65/Male	43/Female	40/Male	23/Female
BMI, kg/m^2	31.6	26.9	21.3	28.5	20.4
Baseline FibroScan, kPa	12.2	4.4	6.8	16.9	7.9
Reason for transplant	Idiopathic pulmonary fibrosis	Pulmonary fibrosis related to Sjögren's syndrome	Idiopathic pulmonary arterial hypertension	A1ATD	Cystic fibrosis
EVLP, yes/no (minutes)	Yes (195)	Yes (315)	No	No	No
Induction therapy	Basiliximab	Basiliximab	Basiliximab	None[a]	None[a]
HCV GT	GT 2	GT 1b	GT 1a	GT 1a	GT 1a
Antiviral regimen	SOF/VEL	LDV/SOF	LDV/SOF	LDV/SOF	LDV/SOF
Time post transplant to antiviral initiation, days	28	94	83	24	24

Abbreviation: A1ATD=α-1 antitrypsin deficiency.
[a]No induction therapy was provided in Participants 4 and 5 due to Epstein-Barr virus mismatch (donor positive and recipient negative).

No AEs were attributable to HCV treatment, and there were no changes in kidney or liver function during study treatment. Post-transplant complications were deemed to be related to the severity of the participants' pre-existing disease states.

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. Cypel M, Feld JJ, Galasso M, et al. Prevention of viral transmission during lung transplantation with hepatitis C-viraemic donors: an open-label, single-centre, pilot trial. *Lancet Respir Med.* 2020;8(2):192-201.
4. Abdelbasit A, Hirji A, Halloran K, et al. Lung Transplantation from Hepatitis C Viremic Donors to Uninfected Recipients. *Am J Respir Crit Care Med.* 2018;197(11):1492-1496.
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
EVLP=ex vivo lung perfusion
GT=genotype
ICU=intensive care unit
LDV=ledipasvir
LFT=liver function test
NAT=nucleic acid test
PCR=polymerase chain reaction
RBV=ribavirin
SAE=serious adverse event
SOF=sofosbuvir
SVR12/24=sustained virologic response 12/24 weeks after end of treatment
VEL=velpatasvir
VL=viral load
VOX=voxilaprevir

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:

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

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