Sofosbuvir/Velpatasvir Single-Tablet Regimen for 12 Weeks in Patients Co-Infected with HCV and HIV-1: The Phase 3 ASTRAL-5 Study

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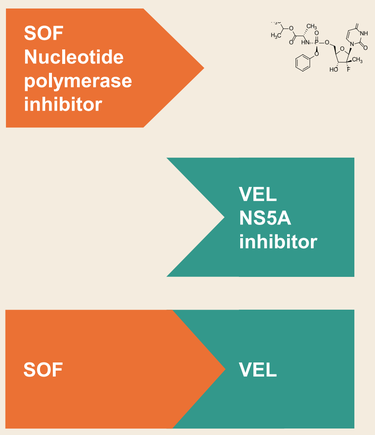
Introduction

- Sofosbuvir (SOF)[1,2]
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet
- Velpatasvir (VEL; GS-5816)[3]
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile
- SOF/VEL FDC[4-6]
  - Once daily, oral, FDC (400/100 mg)
  - Treatment with SOF/VEL for 12 weeks in Phase 3 studies resulted in high SVR in patients with HCV GT 1–6

FDC, fixed-dose combination.

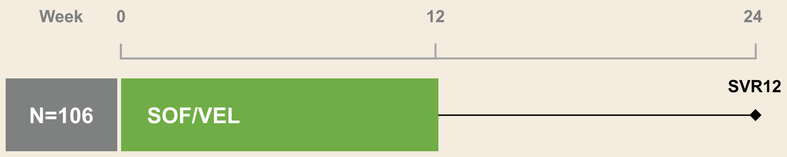


Background

- Liver-related disease remains a major cause of morbidity and mortality in patients coinfected with HCV and HIV-1[7]
  - Accelerated progression of liver disease
  - Higher rates of cirrhosis, end-stage liver disease, and hepatocellular cancer
- Direct-acting antiviral (DAA) therapy that is effective across all HCV genotypes with limited drug-drug interactions with antiretroviral therapy (ART) is needed
- This Phase 3 study aimed to evaluate safety and efficacy of SOF/VEL in patients coinfected with HCV and HIV-1

Methods

Study Design



- Open-label, single-arm, multicenter, Phase 3 study
- Broad inclusion criteria
  - HCV genotypes 1–6
  - Treatment naïve or experienced
  - 30% with compensated cirrhosis
  - On stable ART for ≥8 weeks, CD4 cell count ≥100 cells/mm3, and HIV RNA ≤50 copies/mL
- Inclusion of non-nucleoside reverse-transcriptase inhibitor (NNRTI), integrase inhibitor, and protease inhibitor (PI) regimens with TDF/FTC or ABC/3TC

3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

Study Endpoints

- Primary endpoint: SVR12
  - HCV RNA <LLOQ at post-treatment Week 12
    - COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, v2.0; LLOQ=15 IU/mL
- Safety
  - Adverse events and discontinuations
  - Maintenance of HIV-1 RNA <50 copies/mL
  - Laboratory abnormalities
  - Changes in renal function

Results

Demographics and Baseline Characteristics

	SOF/VEL n=106
Mean age, y (range)	54 (25–72)
Male, n (%)	91 (86)
Black, n (%)	48 (45)
Mean BMI, kg/m^2 (range)	27 (19–43)
Cirrhosis, n (%)	19 (18)
Treatment experienced,* n (%)	31 (29)
IL28B CC, n (%)	24 (23)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.3 (5.0–7.4)
HCV genotype	
1a / 1b	66 (62) / 12 (11)
2	11 (10)
3	12 (11)
4	5 (5)

*Includes PEG + RBV failures and PI + PEG + RBV failures

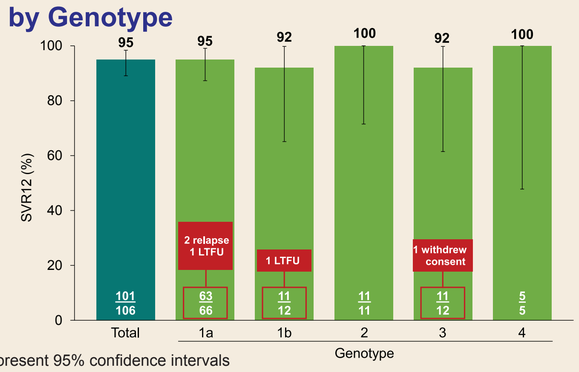
Results

HIV Baseline Characteristics

	SOF/VEL n=106
Mean CD4 count, cells/μL (range)	598 (183–1513)
NRTI backbone	
TDF-based with boosted agent (RTV or COBI)	56 (53)
TDF-based without boosted agent	35 (33)
ABC/3TC-base	15 (14)
ART use at baseline	
PI (DRV, LPV or ATV)	50 (47)
NNRTI (RPV)	13 (12)
Integrase inhibitor (RAL or EVG)	36 (34)
Other (>1 of the above classes)	7 (7)

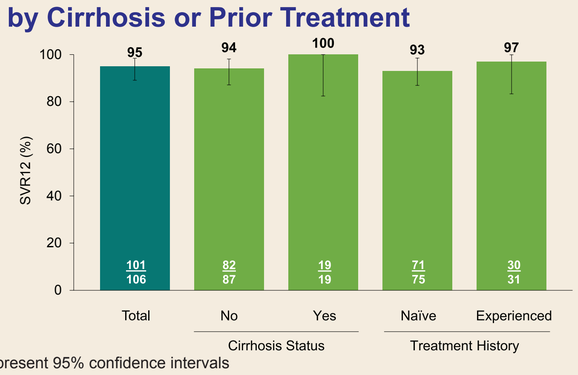
NRTI, nucleoside-analog reverse-transcriptase inhibitor; NNRTI, non-nucleoside analog reverse-transcriptase inhibitor; 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; COBI, cobicistat; DRV, darunavir; EVG, elvitegravir; LPV, lopinavir; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir.

SVR12 by Genotype



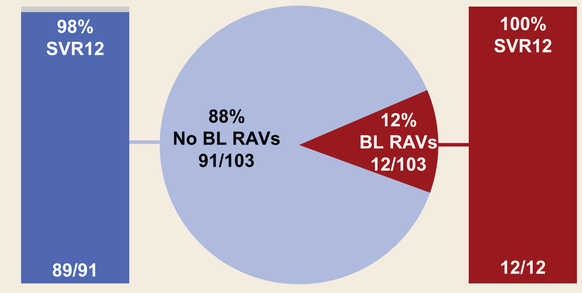
Error bars represent 95% confidence intervals

SVR 12 by Cirrhosis or Prior Treatment



Error bars represent 95% confidence intervals

SVR12 by Baseline NS5A RAVs



NS5A class RAVs; 15% deep-sequencing cut-off.
3 patients without post-treatment samples were excluded from analysis

- All patients with NS5A Class RAVs achieved SVR
  - 1% cutoff: 19/19 patients

Overall Safety

Patients, n (%)	Total N=106
AE	75 (71)
Grade 3−4 AE	9 (8)
Serious AE	2 (2)
D/C due to AE	2 (2)
Death	0
Grade 3 or 4 laboratory abnormality*	19 (18)
HIV virologic rebound	0

*8 out of 19 were elevated total bilirubin; all 8 were on atazanavir/ritonavir

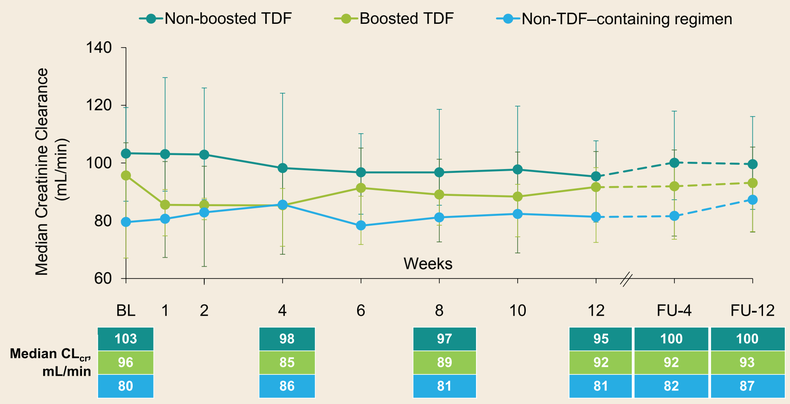
- SAEs: Acute radial nerve palsy and left toe infection/sepsis/UTI, neither deemed related to study drug
- Most common laboratory abnormality was elevated bilirubin in patients receiving atazanavir/ritonavir

Adverse Events in ≥5%

Adverse event, n (%)	Total N=106
Fatigue	26 (25)
Headache	14 (13)
Arthralgia	9 (8)
Upper respiratory tract infection	9 (8)
Diarrhea	8 (8)
Insomnia	7 (7)
Nausea	7 (7)

- The majority of AEs were mild in severity (Grade 1 and 2)

Renal Function



- FU-4/12, follow-up Week 4/12; Creatinine Clearance calculated using the Cockroft-Gault method; error bars represent Q1, Q3.

Conclusions

- SOF/VEL treatment for 12 weeks resulted in 95% SVR12 rate in patients coinfected with HIV and HCV GT 1, 2, 3, and 4
  - –100% SVR12 in patients with cirrhosis
  - –97% SVR12 in patients who failed prior HCV therapy
- Presence of baseline NS5A RAVs did not impact SVR12
- Treatment with SOF/VEL for 12 weeks was safe and well tolerated with ART, including TDF-based with boosted regimens
- SOF/VEL for 12 weeks provides a simple, safe, and highly effective treatment for patients coinfected with HIV-1 and HCV

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