Ledipasvir/Sofosbuvir for 8 Weeks – A Comparative Analysis of Clinical Trial Efficacy Versus Real World Effectiveness

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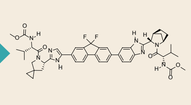
Introduction

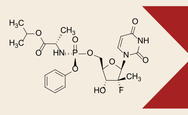
Ledipasvir/Sofosbuvir STR[1-4]

- Ledipasvir (LDV)
  - Picomolar potency against multiple HCV genotypes
  - Effective against NS5B RAV S282T
  - Once-daily, oral, 90 mg

LDV NS5A inhibitor



- Sofosbuvir (SOF)
  - Potent antiviral activity against HCV GT 1–6
  - Effective against NS5A RAVs
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet



SOF - NS5B nucleotide polymerase inhibitor

- Ledipasvir/Sofosbuvir STR
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet, RBV-free

LDV NS5A inhibitor + SOF - NS5B nucleotide polymerase inhibitor

- To date, >250,000 patients treated with LDV/SOF globally

Background

- ION-3 was a phase 3, randomized, open-label study comparing 8 vs. 12 weeks of LDV/SOF in GT 1 treatment-naïve, non-cirrhotic patients
- SVR rates were non-inferior between the 8 and 12 week LDV/SOF arms (94% vs. 96%, respectively)
- Post-hoc analysis showed that the relapse rates in the 8 week arm were comparable to 12 weeks of LDV/SOF in patients with a baseline HCV RNA of <6M IU/ml
- The FDA, EMA and several treatment guidelines have endorsed the 8 week LDV/SOF regimen as a first line treatment option for TN, NC, GT1 patients with HCV RNA <6M IU/ml

Objectives

- Evaluate the effectiveness of LDV/SOF for 8 weeks in real-world datasets
- Compare SVR data from the ION-3 study to several real-world cohorts

Methods

- Three large, prospective, open-label, multicenter real-world cohorts and two retrospective single center real-world cohorts were reviewed
- Cohorts with missing or incomplete baseline demographic data or single center cohorts with less than 50 patients were excluded

Included Studies[5, 8-12]

ION-3 N=123	TARGET N=154	TRIO N=263	GECCO N=245	IFI N=130	VA- Ohio N= 60
ION 3 Study*	HCV-TARGET	TRIO Cohort	GECCO	IFI/ Buggisch	VA-Ohio
	Multicenter: US and Germany			Single center: Germany and US	

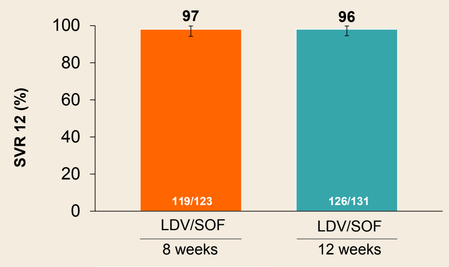
Results

Baseline Demographics

Characteristic	ION-3 N=123	TARGET N=154	TRIO N=263	GECCO N=245	IFI N=130	VA- Ohio N= 60
Median age, years (range)	52 (22-73) ^	58 (19-84)	57 (18-84) ^	50 (17-81)	51 (22-77)	61 (32-75) ^
Male, n (%)	67 (54)	70 (46)	121 (46)	121 (49)	56 (43)	56 (93)
Race, n (%)						
Non black	96 (78)	120 (78)	224 (85)	n/a	128 (99)	27 (46)
Black	27 (22)	34 (22)	39 (15)	n/a	0	33 (54)
HCV GT 4	0	0	0	4	2	0
HCV genotype 1a, n (%)	89 (72)	101 (66)	180 (68)	114 (47)	67 (52)	36 (59)
VL >6 M IU/ml	0	n/a	8	19*	4	0
Treatment Experienced (%)	0	8	0	37 (15)	3	7
HIV/HCV (%)	0	1	0	35 (14)	5	0
Fibrosis Score (liver biopsy), n (%)						
F0-F2	87 (71)	n/a	205 (78)	n/a	120 (93)	n/a
F3	14 (12)	n/a	32 (12)	n/a	10 (7)	n/a
F4	0	n=6	0	n=3 ***	0	0
Unknown/other	22 (17) **	n/a	26 (10)	n/a	0	60^^

* Defined as >6 million with Roche TaQman® v2.0, >2 million with the Abbott Real Time PCR **15% were cirrhotic on FibroTest but confirmed non-cirrhotic with biopsy, 2% had no data, ***Fibro Scan® >12.5 or APRI >2.0, n/a= not available, ^ mean age used, ^^ All patients had fibro scan <12.5 kPa

ION-3 - Efficacy and Relapse with Baseline HCV RNA <6 Million IU/ml[5]

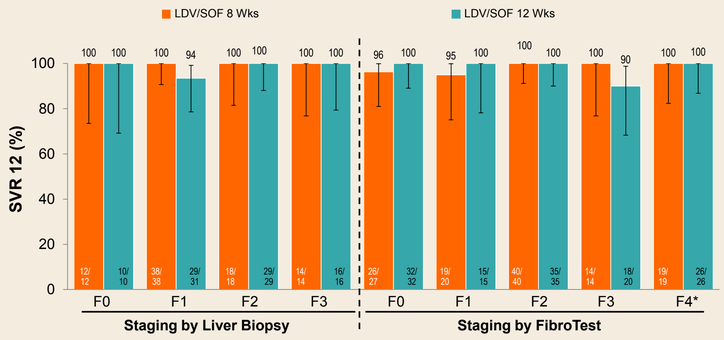


	LDV/SOF 8 weeks	LDV/SOF 12 weeks
Relapse Rates < 6M	1.6% (2/123)	1.5% (2/131)
Relapse Rates ≥ 6M	9.8% (9/92)	1.2% (1/85)

- 8 weeks of LDV/SOF was non-inferior to 12 weeks LDV/SOF for both SVR12 and relapse rates

Results (Cont'd)

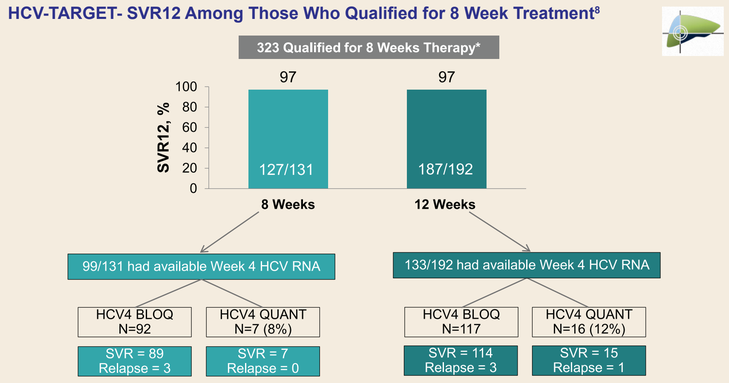
ION-3 - SVR12 by Fibrosis Scores in Patients with Baseline HCV RNA <6 Million IU/mL



* FibroTest is based on quantitative results of 5 serum biochemical markers (alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma glutamyl transpeptidase (GGT) and bilirubin) – can overestimate stage of fibrosis. If patients had discordant biochemical tests, a liver biopsy was used.

- The baseline viral load cut-off of <6 million IU/mL demonstrated high efficacy across fibrosis stages

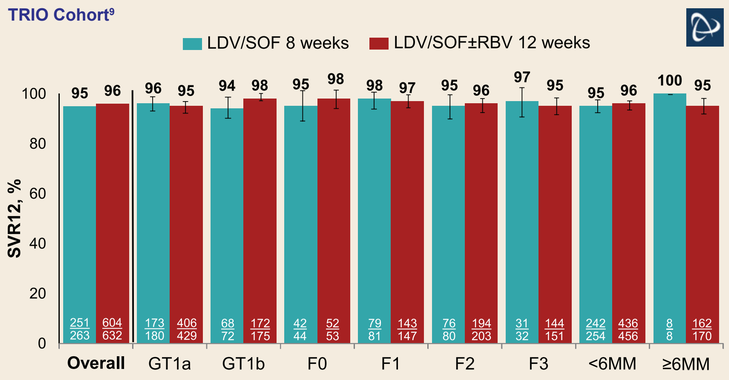
HCV-TARGET- SVR12 Among Those Who Qualified for 8 Week Treatment[8]



*Qualified = Treatment-naïve, no cirrhosis, HCV RNA ≤ 6 million IU/mL

- 323 subjects qualified for 8 week therapy, but only 41% received an 8 week duration

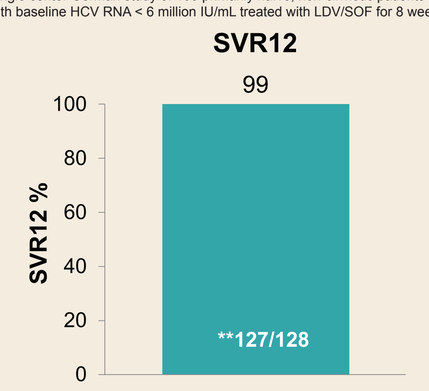
TRIO Cohort[9]



- Overall discontinuation rate was <1% (7/895)

German Real-World LDV/SOF for 8 Weeks[11]

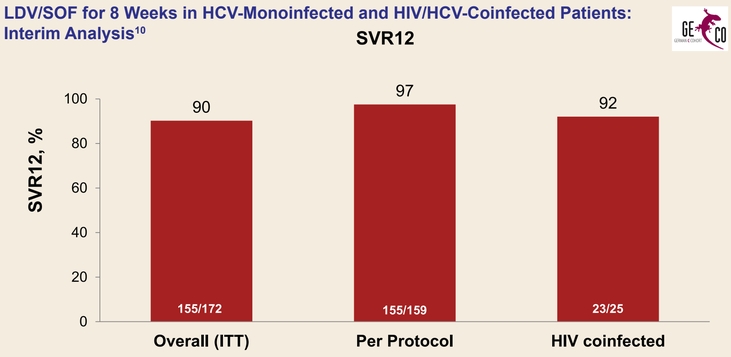
Single center German study of 130 primarily naïve, non-cirrhotic patients with baseline HCV RNA < 6 million IU/mL treated with LDV/SOF for 8 weeks



** 1 male patient with relapse (early relapse week 4 follow up) had good compliance, was not taking proton pump inhibitors, had F3. Q80L and L31M mutations were detected after relapse (no baseline testing performed)
*Roche COBAS® AmpliPrep/COBAS® TaqMan®, cut-off < 12 IU/mL
Fibrosis was measured by FibroScan® with cut-off values for METAVIR stage F3 or less of ≤12.3kPa

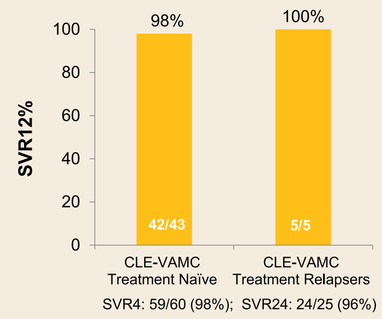
- 52% of all GT1 patients who were selected for treatment were eligible for 8 weeks and were treated for 8 weeks of LDV/SOF

LDV/SOF for 8 Weeks in HCV-Monoinfected and HIV/HCV-Coinfected Patients: Interim Analysis[10]



Real Life Outcomes with LDV/SOF for 8 Weeks in Veterans without Cirrhosis Confirmed by Transient Elastography (TE)[12]

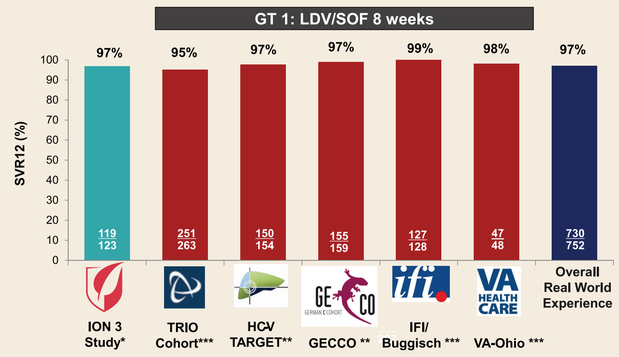
Study of 60 GT 1 TN or PegIFN+RBV relapser Cleveland Veterans (CLE-VAMC) with TE scores < 12.5 kPa and HCV RNA < 6M IU/mL



SVR4: 59/60 (98%); SVR24: 24/25 (96%)

- Using TE score < 12.5 kPa to qualify patients for LDV/SOF for 8 weeks resulted in similar or higher SVR rates than seen in ION-3
- ~$160,000 - 288,000 in saved resources by using TE instead of APRI or FIB-4

SVR12 in ION-3 Compared to Real-World Cohorts[5,8-12]



*Post hoc analysis ** Per Protocol *** ITT analysis

Conclusions

- 8 weeks of LDV/SOF resulted in SVR rates of 97% in multiple, large, real-world cohorts
  - Comparable to the SVR seen in the ION-3 post hoc analysis
  - Real-world patients were more heterogeneous as some do not fit the standard criteria of TN, NC and VL < 6million
- These data confirm the use of the 8 week LDV/SOF regimen, and the validity of the post-hoc analysis that led to the dosing recommendation
- Data from these cohorts suggest that the 8 week regimen is highly efficacious and underutilized in both community and academic centers

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