Sofosbuvir in hemodialysis: 400 mg daily or only the day of hemodialysis?

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Session 8: Oral abstracts
Thursday, 28 May 2015
2:30pm to 3:30pm

Hepatitis C infection in patients with chronic kidney disease (CKD)

- **HCV infection**
  - independent risk factor for CKD development
- **HCV infection in CKD patients**
  - Faster liver disease progression
  - Higher liver-related morbi-mortality
- **Anti-HCV treatment in CKD patients**
  - Reduce significantly proteinuria and stabilized serum creatinine

Chen, YC *et al.*, Kidney Int 2014- EASL, J Hepatol 2014 - Azmi AN, *et al.* World J Hepatol 2015

- **SOF containing-regimen in patients on hemodialysis (HD)***
  - Neither **safety dosing** nor **efficacy data available**
  - Need for **dose adjustments unknown**
  - should not be administered to patients **until more data is available**
  - in France, no reimbursement indication, due to lack of guidelines

*AASLD/IDSA/IAS-USA. Recommendations for Testing, Managing, and Treating Hepatitis C - Unique patient populations: patients with renal impairment 2014 http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-renal-impairment

EASL recommendations on treatment of Hepatitis C 2014, J Hepatol

SOF in CKD patients in the litterature

- **15 VHC GT1 patients** on hemodialysis

  SOF 200mg QD + SMV 150mg QD
  - Safe and well-tolerated
  - 2 relapsers

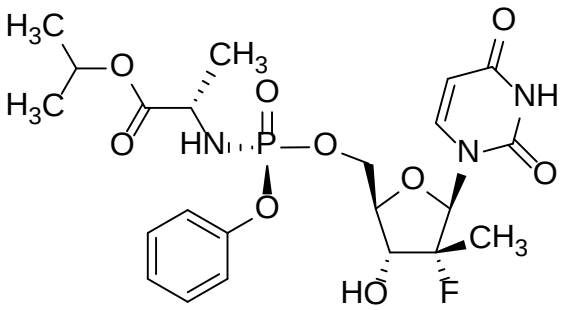
  Bhamidimarri K, et al. EASL 2015
- **9 VHC GT1 or GT3 CKD patients**

  SOF 200mg QD + RBV (VHC 1 or 3)
  - Safe and relatively well tolerated
  - 5 relapsers

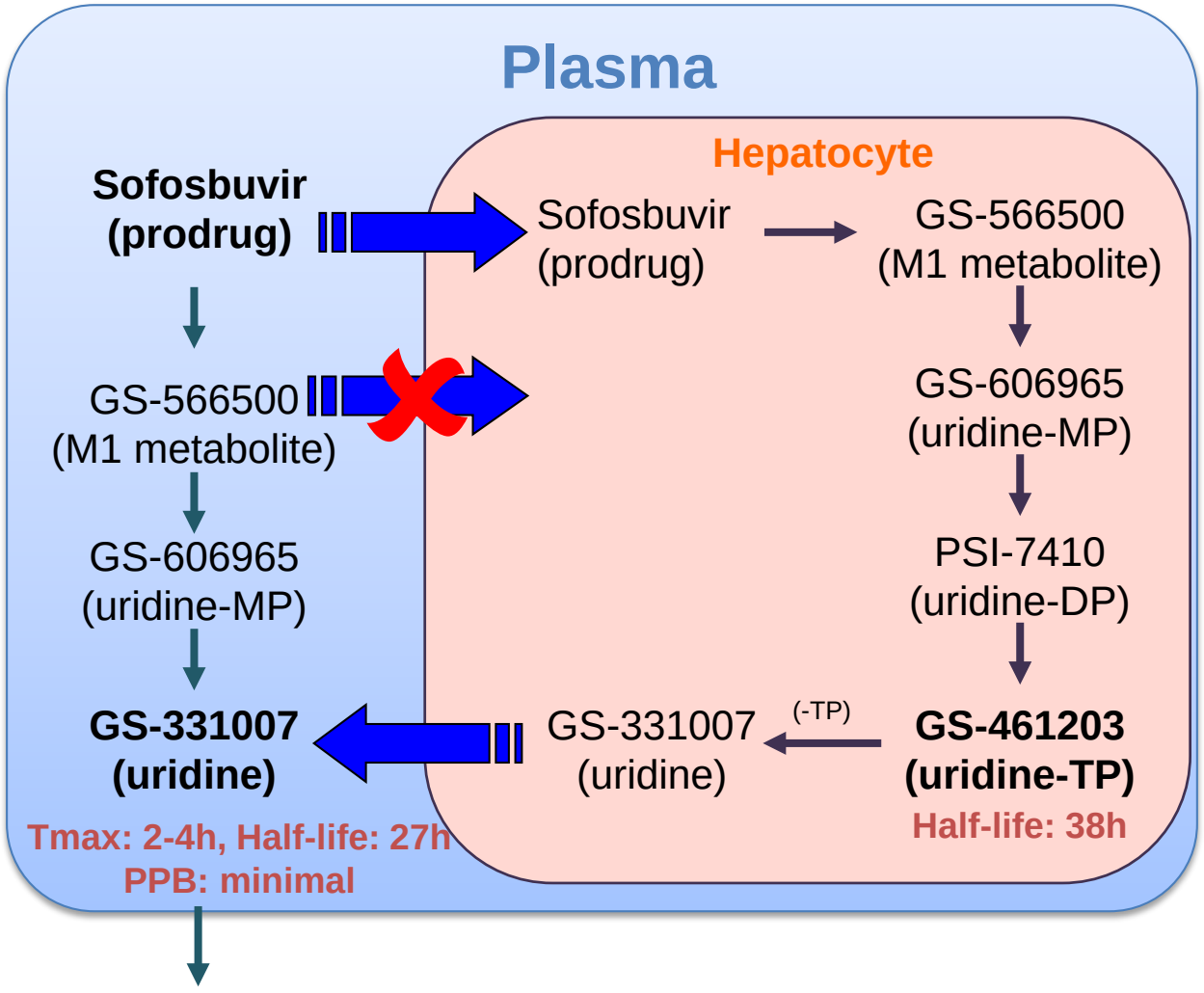
  Gane EJ, et al. AASLD 2014
- **1 HCV GT1 patient on HD** with liver transplantation SOF200mg QD + SMV 150mg QD
  - Safe and well tolerated
  - SVR 12

  Perumpail RB, et al. Transpl Infect Dis 2015

Sofosbuvir pharmacokinetic characteristics

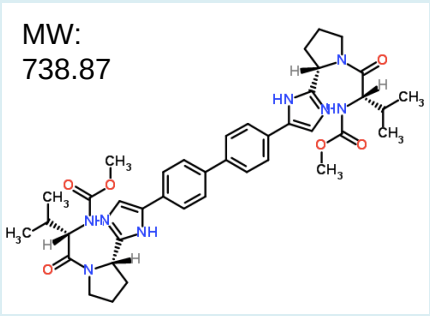
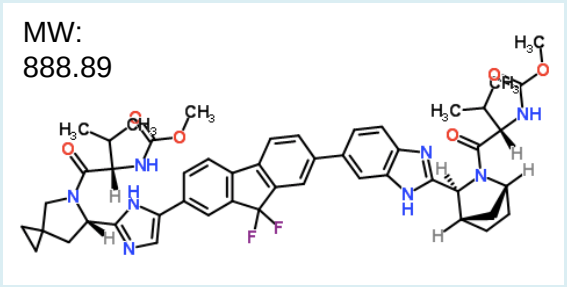
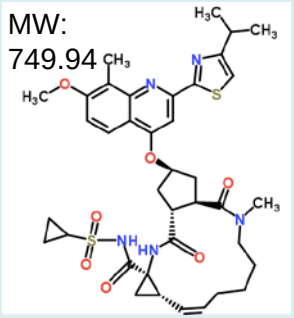


Sofosbuvir
MW = 529.45 g/mol
Tmax: 0.5h-2h
Half-life: 1.5h
Plasma Protein binding (PPB): 61-65%



Ma H, *et al.* J Biol Chem 2007
Sovaldi®, EMA Product Information 2015

Other Direct Acting Anti-HCV Agents useful characteristics

Daclatasvir (DCV)	Ledipasvir (LDV)	Simeprevir (SMV)
		
Biliary excretion	Biliary excretion	Biliary excretion
PPB>99%, Half-life: 15h	PPB>99,8%, Half-life: 47h	PPB>99,9% Half-life: 41h
No dose adjustment of Daklinza® is required for patients with any degree of renal impairment	Hemodialysis is unlikely to result in significant removal of ledipasvir	As exposure may be increased in HCV infected patients with severe renal impairment, caution is recommended when prescribing simeprevir to these patients

Daklinza® EMA Product Information 2014, Harvoni® EMA Product Information 2015, Olysio® EMA Product Information 2015

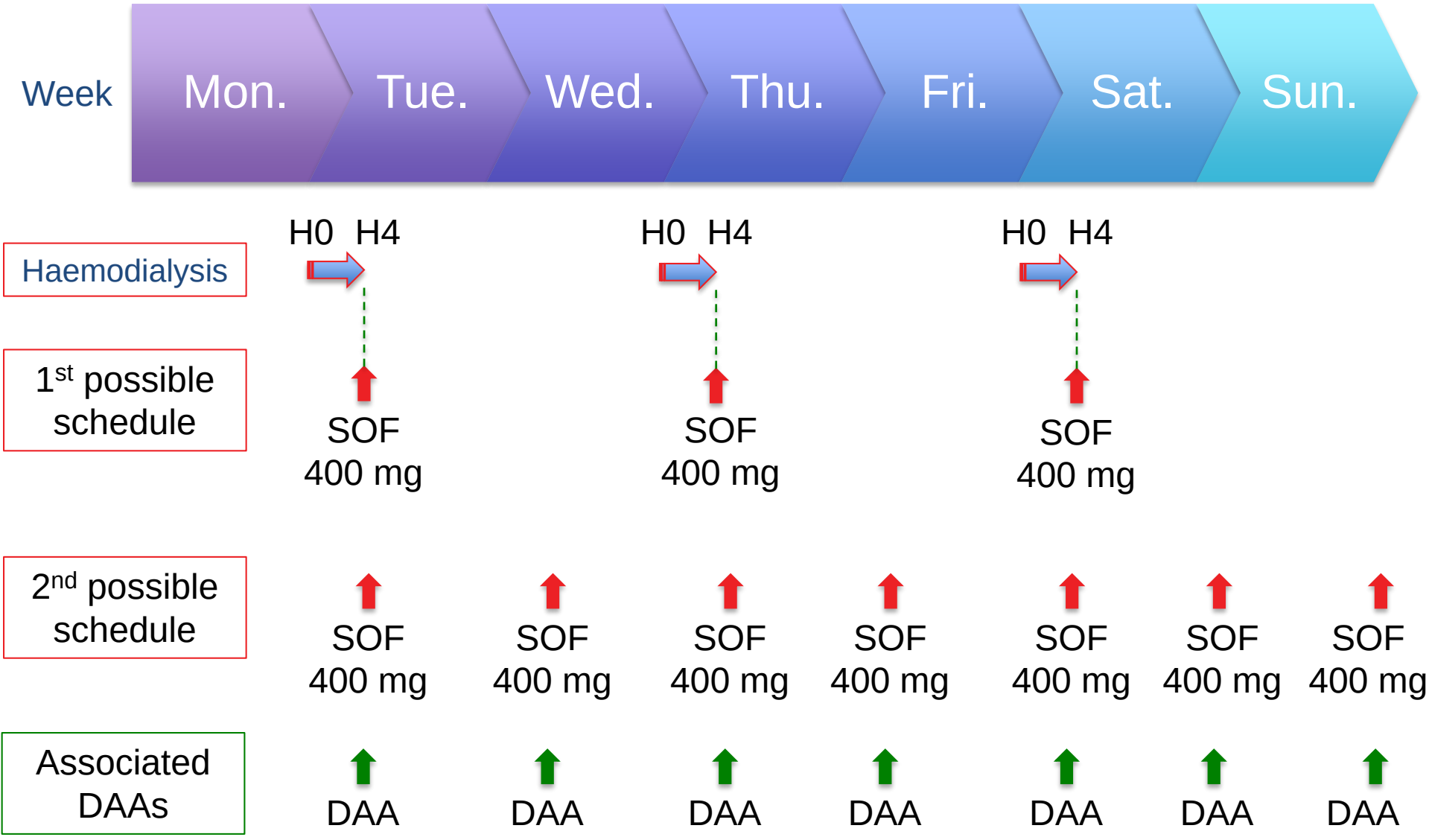
Objectives

- To determine safety, efficacy and pharmacokinetics parameters of SOF, SOF-007 and associated DAAs in HCV-infected patients requiring hemodialysis (HD)
  - receiving SOF **400mg three times a week** (TIW) after HD
  - receiving SOF **400mg once-daily** (QD) after HD

Materials and Methods (1)

- **Prospective, multicenter and observational study**
- **Inclusion criteria**
  - HCV-infected patients on HD requiring anti-HCV treatment
  - Naive, null or partial responders to previous anti-HCV treatment (PegIFN + Ribavirin +/- boceprevir)
  - Receiving SOF containing-regimen combined with :
    - daclatasvir (DCV) 60mg once-daily (QD),
    - Or ledipasvir (LDV) 90mg QD,
    - Or simeprevir (SMV) 150mg QD,
    - Or ribavirine (RBV) 200mg QD

Study design



Materials and methods (2)

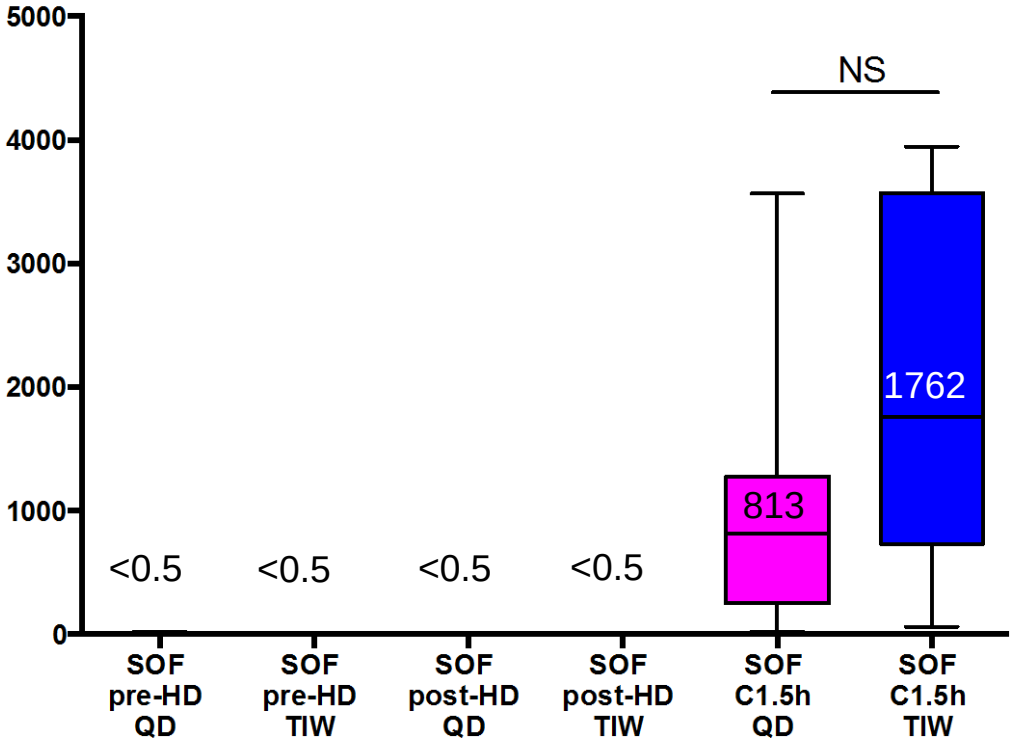
- Blood samples were collected **before HD (Pre-HD), after a 4hour-HD (Post-HD) and 1.5 hour after dose intake (C1.5h)** after the end of HD
- **Plasma concentrations** of **SOF, SOF-007, RBV, SMV, DCV** and **LDV** were determined using UPLC-MS/MS (Waters Acquity UPLC-TQD, Milford, MA, USA)
- **Lower limit of quantification** (LOQ) was 1 ng/ml for SOF and 10 ng/mL for other compounds
- **Dialysance:** determined using paired pre and post-HD plasma concentration [(pre-HD - Post-HD)/Pre-HD]
- **Accumulation of SOF-007:** Spearman's correlations tests between plasma concentrations and days of cumulated treatment
- **Statistical analysis:**
  - Descriptive analysis: median (IQR25-75%)
  - Non-parametric Mann-Whitney tests
  - Wilcoxon matched-pairs signed rank test

Patients characteristics

Patients, n (Men)	13 (11)
Samples, n (Before HD; After HD; 1.5hr post-dose)	256 (100;81;75)
Age, years, median (IQR)	52.0 (43.5-60.8)
Race/ethnicity, n	
Caucasian	8
African	4
Asian	1
HCV genotype, n	
1 / 2 / 3/ Unknown	10 / 1 / 1 / 1
Cirrhosis, n	8
Fibroscan®, kPa (IQR range)	12.2 (1.6-7.9)
Fibrotest, n	
0.00-0.21 (F0)	1
0.22-0.31 (F1)	2
0.59-0.72 (F3)	2
0.75-1.00 (F4)	2
Not determined	6

Contamination mode, n	
IV drug use	3
Iatrogenic	4
Unknown	6
HCV viral load at baseline, Log10 IU/L, median (IQR)	6.47 (5.94-6.76)
HIV/HCV co-infection, n	3
Previous anti-HCV treatment, n	
Naive	7
Null responders	4
Relapsers	2
Anti-HCV regimen, n	
400mg SOF TIW / SOF QD	5/8
+ DCV	9
+ LDV	1
+ SMV	2
+ RBV	1

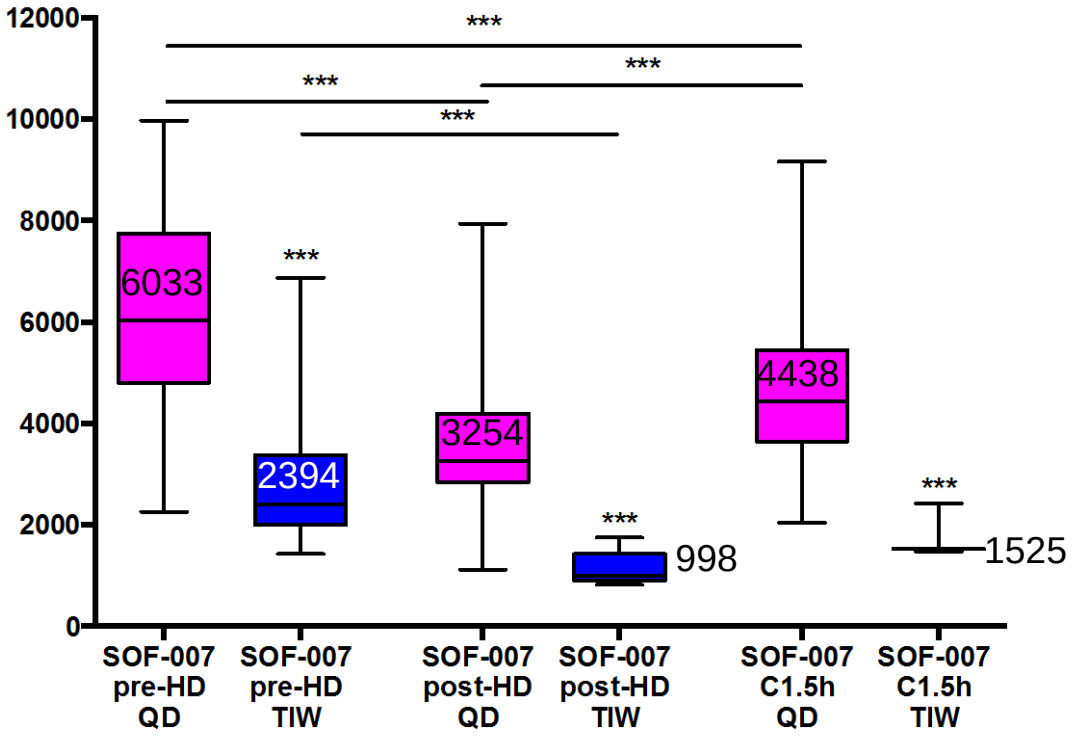
SOF plasma concentrations (median, ng/mL)



	SOF pre-HD QD	SOF pre-HD TIW	SOF post-HD QD	SOF post-HD TIW	SOF C1.5h QD	SOF C1.5h TIW
Patients (n)	5	8	5	8	4	6
Samples (n)	13	87	12	69	5	54

No SOF accumulation pre- and post-HD either in TIW nor in QD patients

SOF-007 plasma concentrations (median,ng/mL)

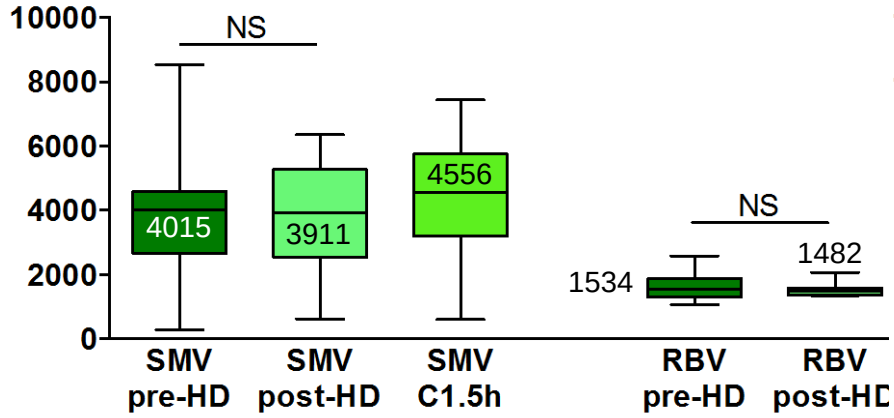


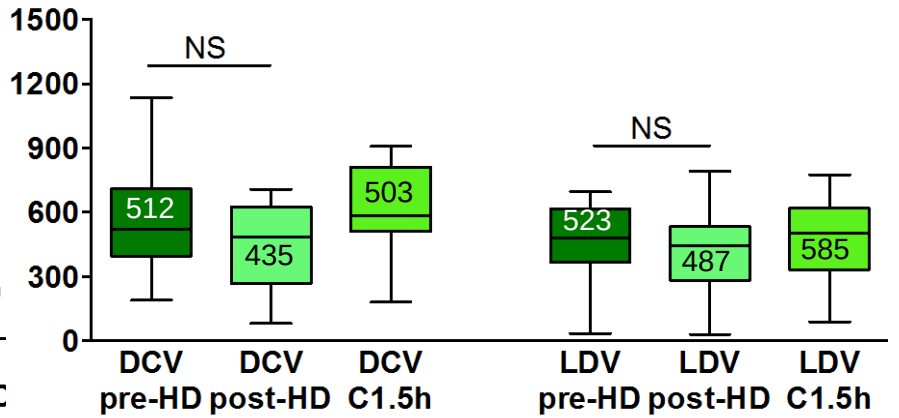
Patients (n)	6	3	6	3	6	3
Samples (n)	68	11	65	11	61	3

65 paired pre- and post-HD samples

SOF-007 Estimated extraction ratio: 52%

Other anti-HCV plasma concentrations (median, IQR; ng/ml)

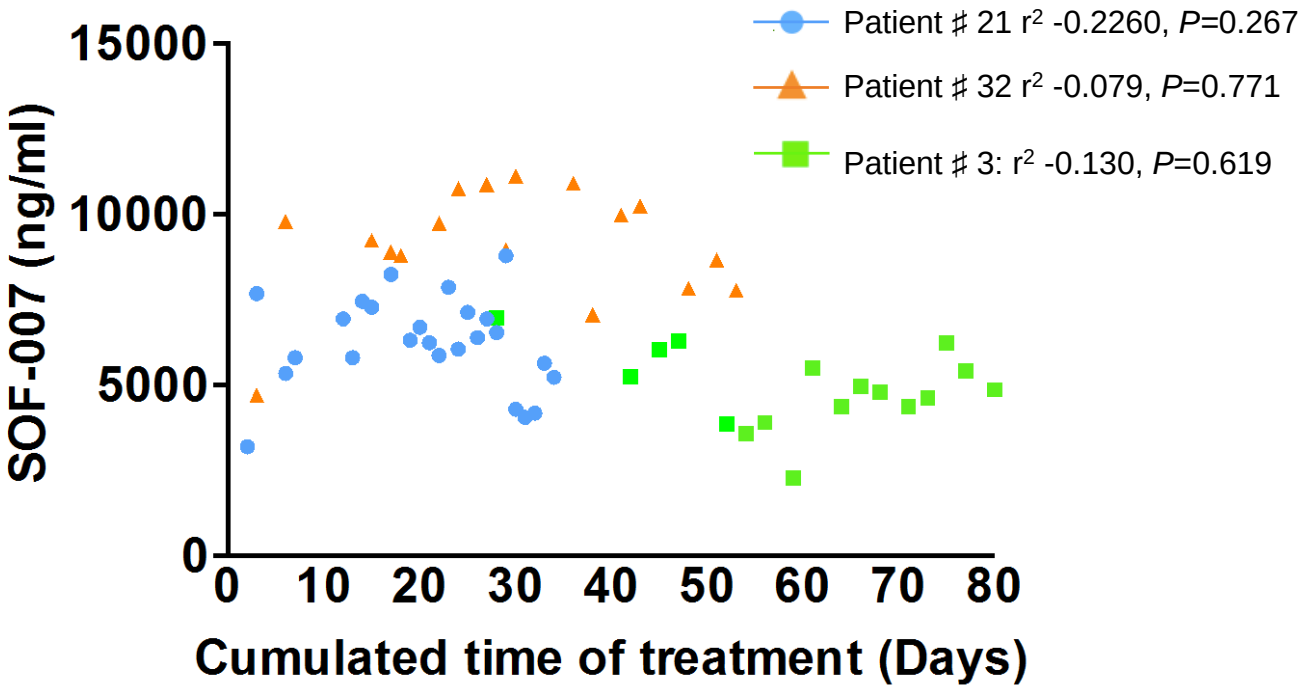




	SMV pre-HD	SMV post-HD	SMV C1.5h	RBV pre-HD	RBV post-HD	DCV pre-HD	DCV post-HD	DCV C1.5h	LDV pre-HD	LDV post-HD	LDV C1.5h
Patients (n)	2	2	2	1	1	8	8	4	1	1	1
Samples (n)	51	36	34	7	7	11	10	7	16	22	21

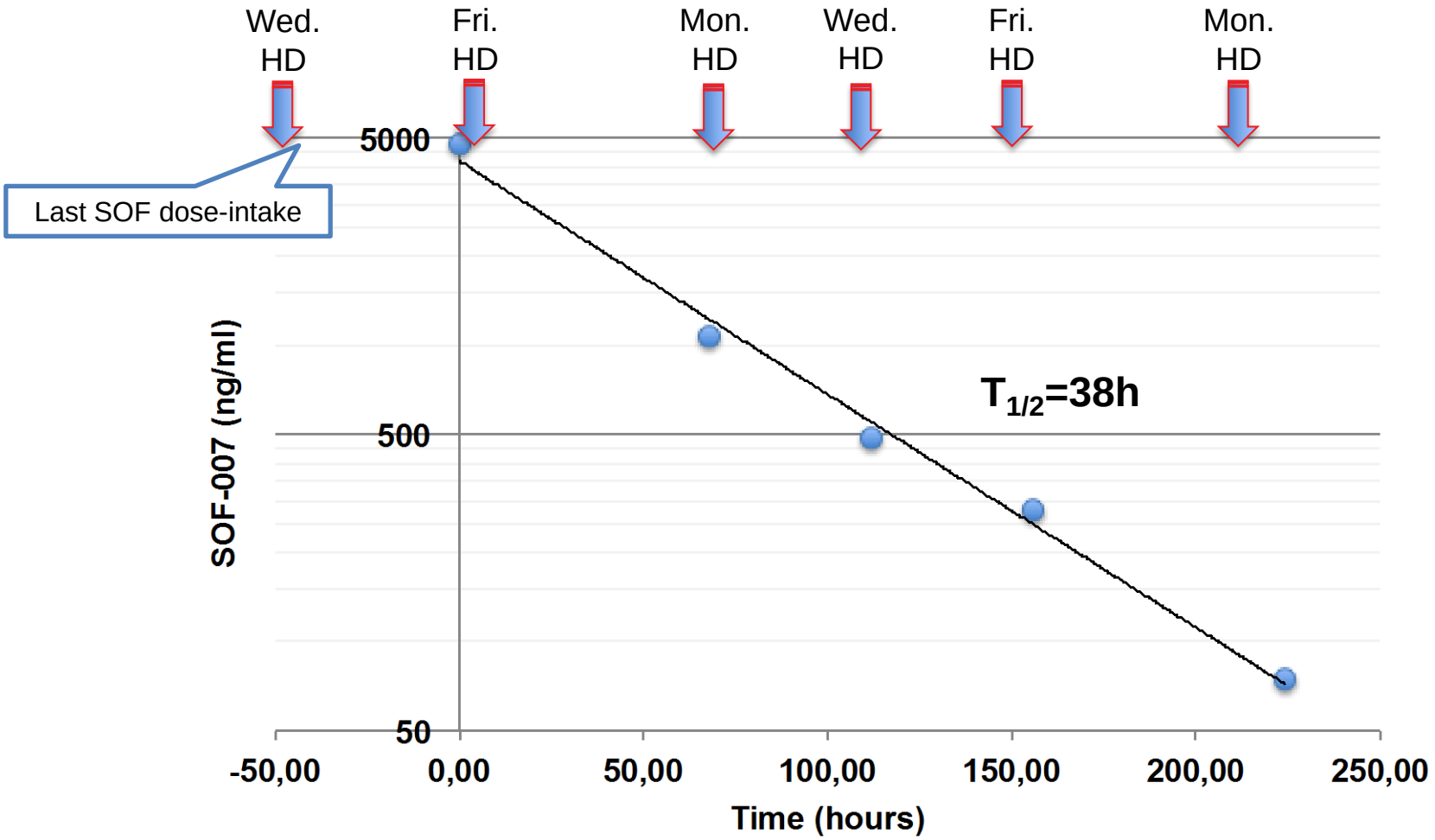
No difference between Pre-HD and Post-HD concentrations for associated DAAs

No SOF-007 accumulation before HD in patients receiving SOF QD



No SOF-007 accumulation between hemodialysis sessions and during the treatment in 3 QD regimen patients

SOF-007 elimination after DAAs cessation (SOF + SMV) in one patient



SOF-007 plasma half-life estimated: 38 h

Patients' tolerance

Median Biological parameters (IQR)

	Before treatment	After treatment	P
AST U/L	39.0 (28.5-75.0)	17.0 (15.0-24.8)	**0.0078**
ALT U/L,	38.0 (26.5-83.5)	14.5 (12.5-23.8)	**0.0039**
Total plasma Bilirubin, mg/dl	7.0 (5.3-8.5)	5.8 (5.0-15.5)	0.6875
GGT U/L	118.0 (61.0-448.0)	53.0 (40.3-128.0)	**0.0039**
Platelet G/L	169.0 (121.5-274.0)	186.5 (172.0-274.5)	0.2109

Clinical Safety

Adverse events	Grade 1	Grade 3
Headache	2	
Muscle weakness	1	
Streptococcus sepsis on erysipelas (unrelated to treatment)		1

Tolerance was very good in all patients

Virological responses

	SVR4	SVR8	SVR 12	SVR 24	Relapse	Pending
SOF TIW		1	1		0	3
SOF QD	1		3	1	0	3

So far no relapse patients, 7 patients with a sustained viral response

Discussion

- SOF C1.5h and SOF-007 **higher** in HD patients than in normal renal function patients*
- But **no SOF and SOF-007 accumulation** in HCV-patient requiring HD neither in SOF TIW nor QD
- SOF-007 extraction ratio consistent with historical data (53%)*
- As expected, HD did not significantly remove SMV, DCV, LDV and RBV*
- Both regimens, TIW and QD were **very well tolerated**
- SOF-007 half-life in a QD patient slightly higher than in normal renal function patients*, but **compatible with a SOF daily-administration**

*Sovaldi®, EMA Product Information 2015 Daklinza® EMA Product Information 2014, Harvoni® EMA Product Information 2015, Olysio® EMA Product Information 2015

Conclusion

- In patient on hemodialysis requiring anti-HCV treatment a regimen containing full-dose SOF is an alternative option
- A close monitoring of these patients should be carried out including clinical, biological, cardiac and therapeutic drug monitoring