ADVANCES IN CHRONIC HEPATITIS C:
MANAGEMENT AND TREATMENT

INDEPENDENT REPORTING ON AASLD 2016

COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

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Safety and Efficacy of the Fixed-Dose Combination Regimen of MK-3682/Grazoprevir/MK-8408 in Cirrhotic or Non-cirrhotic Patients with Chronic HCV GT1 Infection who Previously Failed a Direct-acting Antiviral Regimen (C-SURGE)

David L. Wyles, Heiner Wedemeyer, K. Rajender Reddy, Anne Luetkemeyer, Ira M. Jacobson, John M. Vierling, Stuart C. Gordon, Ronald Nahass, Stefan Zeuzem, Janice Wahl, Eliav Barr, Bach-Yen T. Nguyen, Michael Robertson, Shuyan Wan[1], Patricia Jumes, Frank Dutko, Elizabeth Martin

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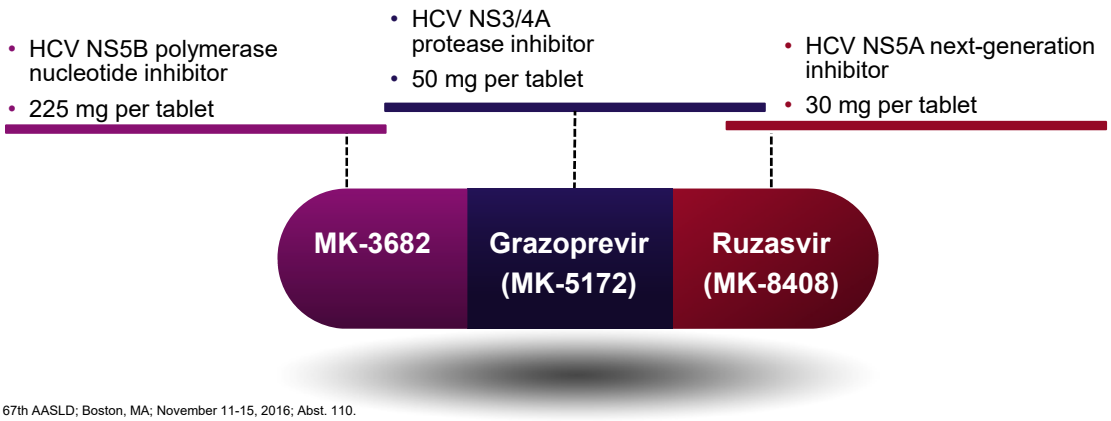
C-SURGE: MK-3682/Grazoprevir/Ruzasvir

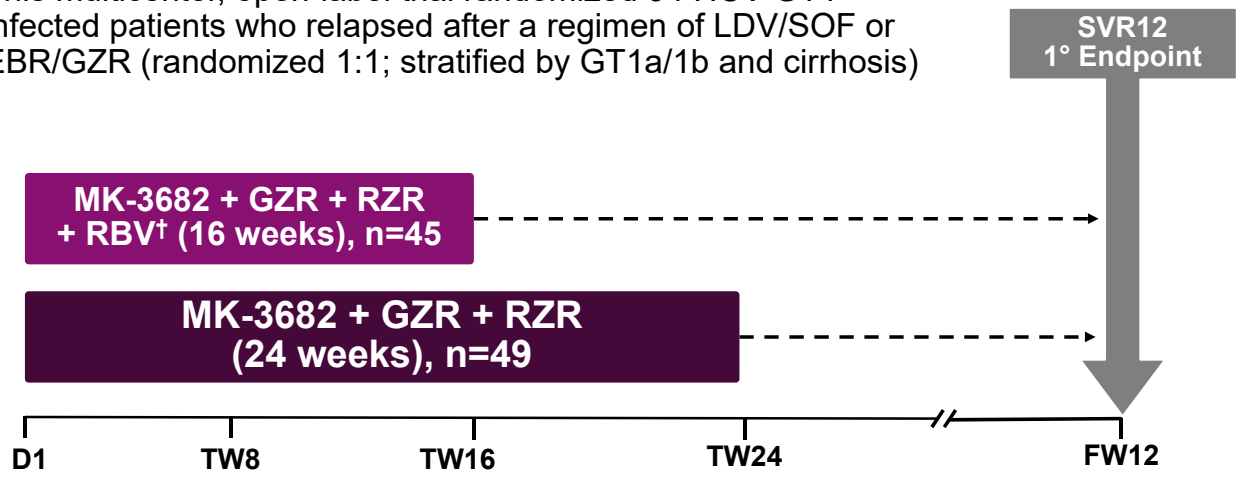
- MK3 is a three-drug regimen formulated into a fixed-dose combination tablet. The regimen is given as two tablets, once-daily, without regard to food
- Triplet also called MK-3682B



Lawitz E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 110.

C-SURGE: Study Design

- This multicenter, open-label trial randomized 94 HCV GT1-infected patients who relapsed after a regimen of LDV/SOF or EBR/GZR (randomized 1:1; stratified by GT1a/1b and cirrhosis)



Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 193.

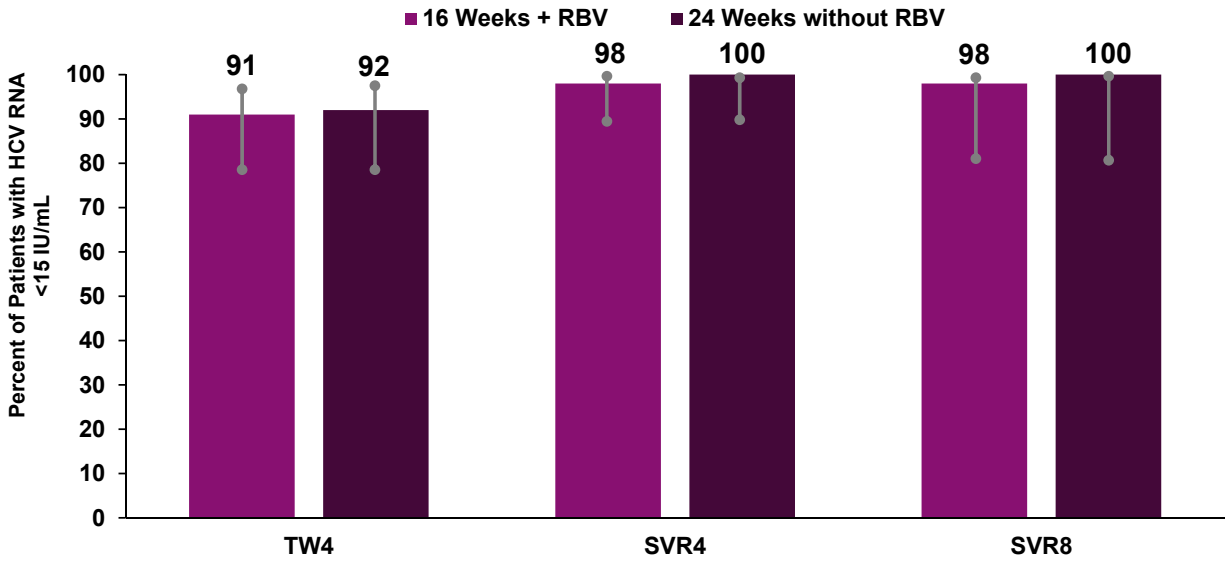
C-SURGE: Study Demographics

Demographics	16 Weeks + RBV, n=44*	24 Weeks without RBV, n=49	Overall GT1 N=93*
Male, n (%)	37 (84)	43 (88)	80 (86)
Age, median years, (range)	61.0 (33 to 70)	60.0 (25 to 71)	60.0 (25 to 71)
Race, White, n (%)	31 (71)	37 (76)	68 (73)
HCV Genotype 1a, n (%)	40 (90)	40 (82)	80 (86)
Non-cirrhotic, n (%) **Cirrhotic, n (%)**	25 (57) 19 (43)	29 (6) 20 (41)	54 (58) 39 (42)
NS5A RAVs at baseline, n (%)† **NS3 RAVs at baseline, n (%)‡**	32 (79) 25 (57)	46 (94) 35 (71)	78 (84) 60 (65)
Baseline HCV RNA >800,00 IU/mL, n (%)	35 (80)	44 (90)	79 (85)
Median baseline HCV RNA (log_{10} IU/mL)	6.5	6.4	6.5
Previously failed: **12 – 24 weeks of LDV/SOF** **8 weeks of LDV/SOF** **12 weeks of EBR/GZR**	 26 (59) 9 (21) 9 (21)	 31 (63) 5 (10) 13 (27)	 57 (61) 14 (15) 22 (24)

RAVs detected by next generation sequencing performed with a 15% sensitivity threshold.
* Does not include 1 patient in the 16 week + RBV arm who withdrew prior to beginning treatment.
Cirrhosis = Liver biopsy at any time showing cirrhosis, Fibroscan result of >12,5kPa within 12 months of enrollment, or Fibrotest >0.75 and APRI >2 at time of enrollment
† NS5A RAVs = any change from wild-type at 4 positions (28, 30, 31, or 93)
‡ NS3 RAVs = any change from wild-type at 14 positions (36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175)

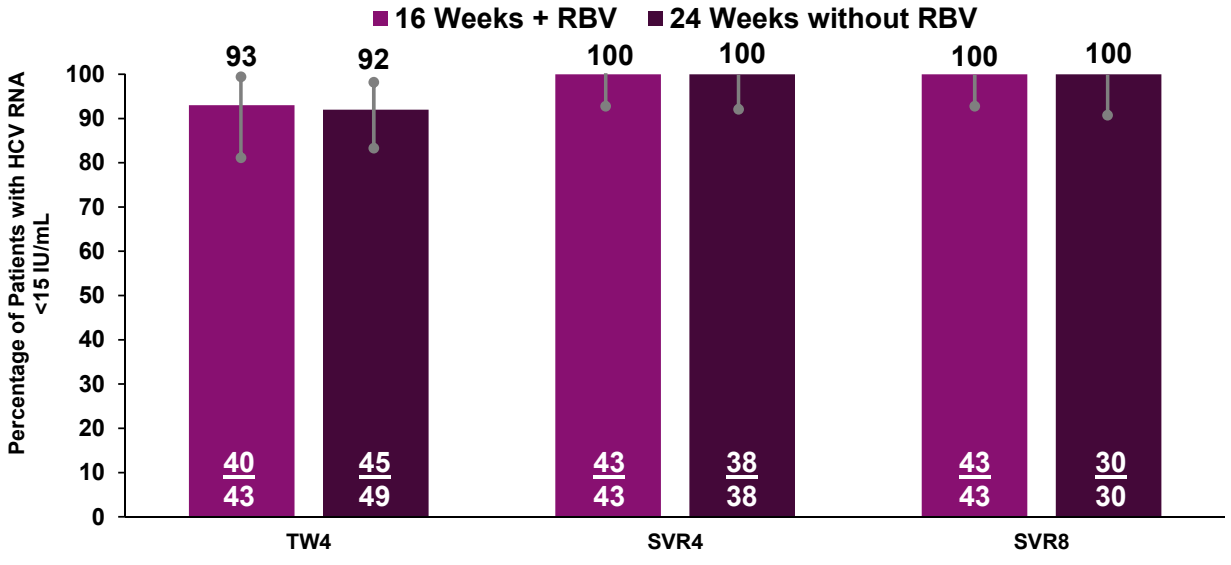
Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 193.

C-SURGE: Results – Efficacy (Full Analysis Set)



Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 193.

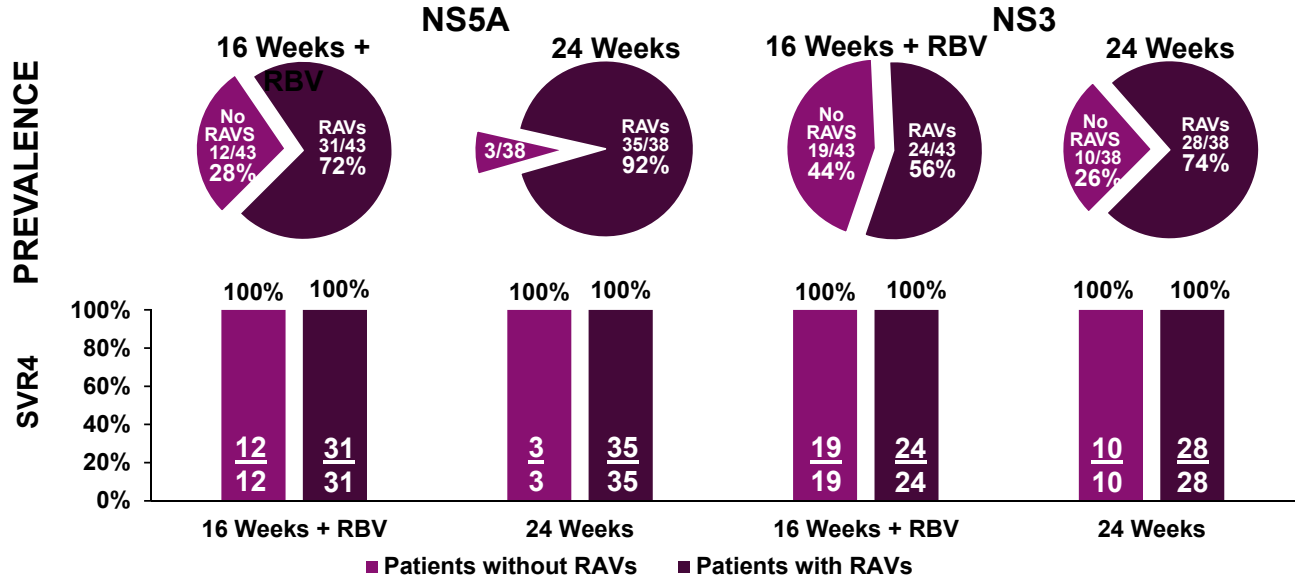
C-SURGE: Efficacy (mFAS*)



TW =treatment week; SVR4 = % of patients with HCV RNA <15 IU/mL at 4 weeks after end of treatment
*Excludes 1 patient from the 16-week + RBV arm who withdrew after receiving 3 doses of study medication

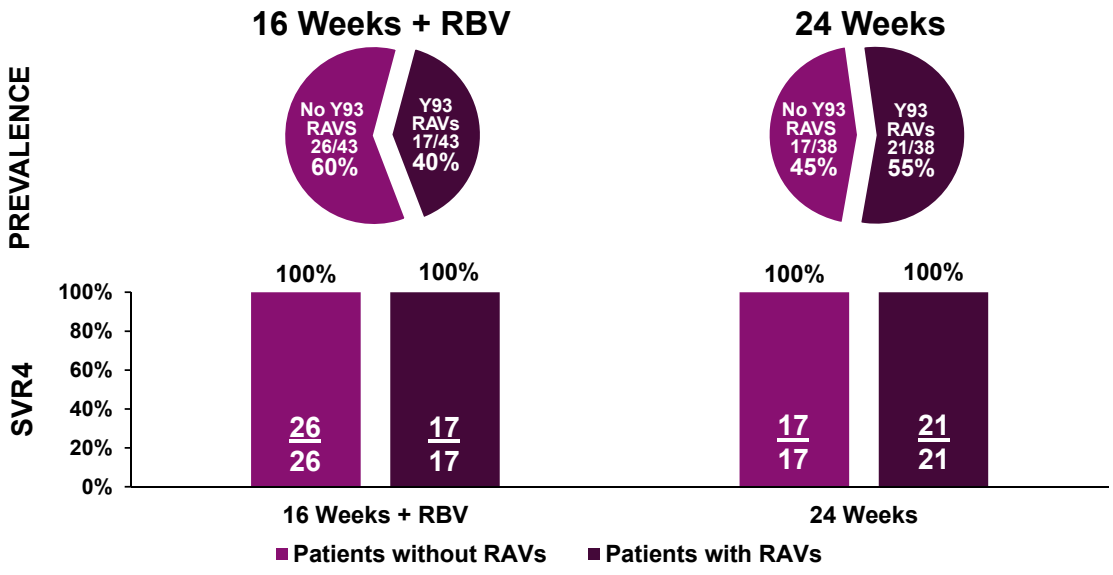
Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 193.

C-SURGE: No Impact of Baseline NS5A or NS3 RAVs on SVR4 (Resistance Analysis Population)



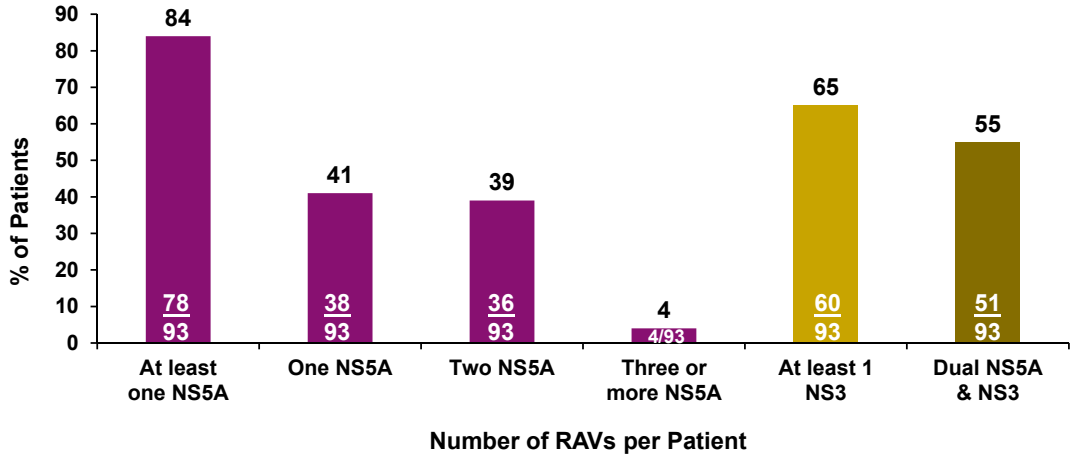
Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 193.

C-SURGE: No Impact of Baseline Y93 RAVs in NS5A on SVR4 (Resistance Analysis Population)



Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 193.

C-SURGE: Baseline NS5A or NS3 RAVs



- RAVs at NS3 position Q80K detected in 33 of 93 patients (35%)
- One patient in the 16 week + RBV treatment group had an NS3 RAV at the 168 position
  - No patients had NS3 RAVs at the 156 position

*RAVs detected by next-generation sequencing with 15% sensitivity; NS5A RAV: any change from wild-type at 4 positions (28, 30, 31, or 93); NS RAVs = any change from wild-type at 14 positions (36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175).

Wyles D, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 193.

Conclusions

- MK3 (MK-3682/grazoprevir/ruzasvir) ± ribavirin was highly effective in cirrhotic and non-cirrhotic GT1 patients who previously failed an NS5A inhibitor-containing direct-acting antiviral regimen
- 98% (43/44) of patients received MK3 + ribavirin for 16 weeks achieved SVR8
  - One patient withdrew from the study after receiving 3 doses
- To date, 100% (38/38) of patients receiving MK3 alone for 24 weeks have achieved SVR4, and 100% (30/30) have achieved SVR8
- High efficacy was observed despite a high prevalence of baseline NS3 and NS5A RAVs in this population
- Treatment was generally safe and well-tolerated

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High Sustained Virologic Response (SVR) Rates in Patients with Chronic HCV GT1, 2 or 3 Infection Following 16 Weeks of MK-3682/Grazoprevir/MK-8408 Plus Ribavirin After Failure of 8 Weeks of Therapy (Part C of C-CREST-1 & 2)

Lawrence Serfaty, Stephen Pianko, Ziv Ben Ari, Alex L. Laursen, Jesper Hansen, Edward J. Gane, Hsueh-cheng Huang, Shu Jin, Jennifer Bourque, Doreen Fernsler, Shuyan Wan, Frank Dutko, Bach-Yen T. Nguyen, Janice Wahl, Eliav Barr, Joan R. Butterton

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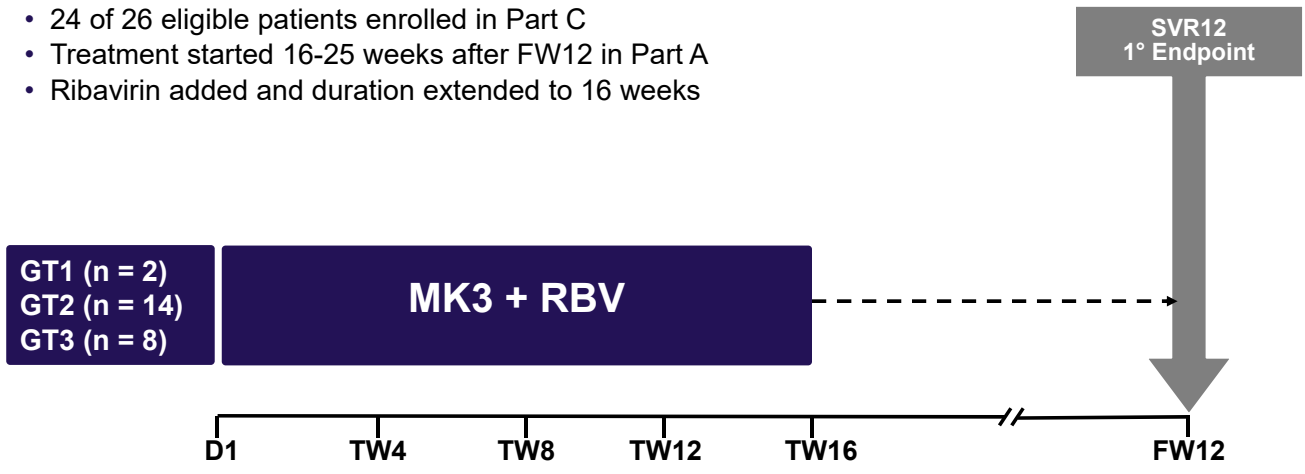
C-CREST 1&2 (Part C): Study Design

- Retreatment of patients who relapsed in Part A (Dose-finding study)
  - 24 of 26 eligible patients enrolled in Part C
  - Treatment started 16-25 weeks after FW12 in Part A
  - Ribavirin added and duration extended to 16 weeks



Serfaty L, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 112.

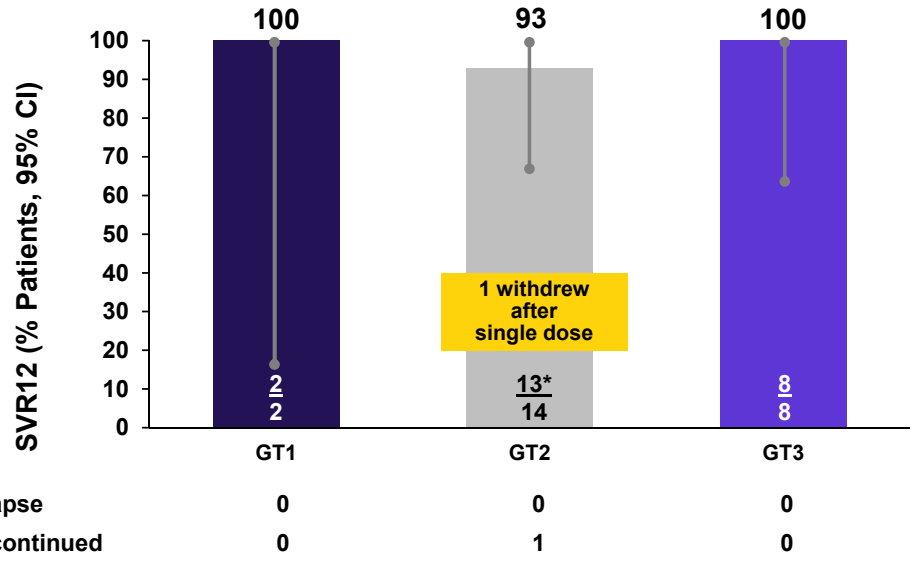
C-CREST 1&2 (Part C): RAVs at Retreatment

GT	Frequency of RAVS at Retreatment, n/N (%)		High-Impact RAVs (>5-fold Reduction in Susceptibility), n/N (%)	
GT1	NS3: NS5A: NS5B:	1/2 (50%) 0/2 (0%) 1/2 (50%)		
GT2	NS3: NS5A: NS5B:	14/14 (100%) 13/14 (0%) 0/14 (0%)	NS35A 31I/M:	11/14 (79%)
GT3	NS3: NS5A: NS5B:	8/8 (100%) 7/8 (88%) 0/8 (0%)	NS3 Q168R: NS5A A30K: NS5A L31M: NS5A S62L: NS5A Y93H:	1/8 (13%) 3/8 (38%) 1/8 (13%) 2/8 (25%) 5/8 (63%)

- All RAVs observed at time of failure in Part A were also detected at initiation of retreatment
- 88% (21/24) patients had RAVS in >1 class

Serfaty L, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 112.

C-CREST 1&2 (Part C): SVR12 by Genotype



Serfaty L, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 112.

C-CREST 1&2 (Part C): Conclusions

- MK3 (MK-3682/grazoprevir/ruzasvir) plus RBV for 16 weeks was highly effective in GT1, 2, and 3-infected patients without cirrhosis who had previously failed 8 weeks of treatment with a 3-DAA regimen
  - 100% SVR12 and 23 patients who completed treatment
- High efficacy despite a high prevalence of baseline NS3 and NS5A RAVs in this DAA failure population
- Treatment was generally safe and well-tolerated