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)


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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

- MK-3682
  - HCV NS5B polymerase nucleotide inhibitor
  - 225 mg per tablet

- Grazoprevir (MK-5172)
  - HCV NS3/4A protease inhibitor
  - 50 mg per tablet

- Ruzasvir (MK-8408)
  - HCV NS5A next-generation inhibitor
  - 30 mg per tablet

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)

MK-3682 + GZR + RZR + RBV† (16 weeks), n=45

MK-3682 + GZR + RZR (24 weeks), n=49

SVR12 1° Endpoint

C-SURGE: Study Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>16 Weeks + RBV, n=44*</th>
<th>24 Weeks without RBV, n=49</th>
<th>Overall GT1 N=93*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>37 (84)</td>
<td>43 (88)</td>
<td>80 (86)</td>
</tr>
<tr>
<td>Age, median years, (range)</td>
<td>61.0 (33 to 70)</td>
<td>60.0 (25 to 71)</td>
<td>60.0 (25 to 71)</td>
</tr>
<tr>
<td>Race, White, n (%)</td>
<td>31 (71)</td>
<td>37 (76)</td>
<td>68 (73)</td>
</tr>
<tr>
<td>HCV Genotype 1a, n (%)</td>
<td>40 (90)</td>
<td>40 (82)</td>
<td>80 (86)</td>
</tr>
<tr>
<td>Non-cirrhotic, n (%)</td>
<td>25 (57)</td>
<td>29 (6)</td>
<td>54 (58)</td>
</tr>
<tr>
<td>Cirrhotic, n (%)</td>
<td>19 (43)</td>
<td>20 (41)</td>
<td>39 (42)</td>
</tr>
<tr>
<td>NS5A RAVs at baseline, n (%)†</td>
<td>32 (79)</td>
<td>46 (94)</td>
<td>78 (84)</td>
</tr>
<tr>
<td>NS3 RAVs at baseline, n (%)‡</td>
<td>25 (57)</td>
<td>35 (71)</td>
<td>60 (65)</td>
</tr>
<tr>
<td>Baseline HCV RNA &gt;800,00 IU/mL, n (%)</td>
<td>35 (80)</td>
<td>44 (90)</td>
<td>79 (85)</td>
</tr>
<tr>
<td>Median baseline HCV RNA (log_{10} IU/mL)</td>
<td>6.5</td>
<td>6.4</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Previously failed:
- 12 – 24 weeks of LDV/SOF
- 8 weeks of LDV/SOF
- 12 weeks of EBR/GZR

† NS5A 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.

* 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)**

![Graph showing efficacy results for C-SURGE](image)

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

**C-SURGE: Efficacy (mFAS*)**

![Graph showing efficacy results for C-SURGE](image)

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)

**NS5A**
- 16 Weeks + RBV
  - No RAVS 12/43 (28%)
  - RAVS 31/43 (72%)
- 24 Weeks
  - RAVS 3/38 (92%)

**NS3**
- 16 Weeks + RBV
  - No RAVS 19/43 (44%)
  - RAVS 24/43 (56%)
- 24 Weeks
  - RAVS 10/38 (26%)

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)

**16 Weeks + RBV**
- No Y93 RAVS 26/43 (60%)
- Y93 RAVS 17/43 (40%)

**24 Weeks**
- No Y93 RAVS 17/38 (45%)
- Y93 RAVS 21/38 (55%)

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

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
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

GT1 (n = 2)
GT2 (n = 14)
GT3 (n = 8)

MK3 + RBV

D1 TW4 TW8 TW12 TW16 FW12

SVR12 1st Endpoint

Serfaty L, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 112.
### C-CREST 1&2 (Part C): RAVs at Retreatment

<table>
<thead>
<tr>
<th>GT</th>
<th>Frequency of RAVS at Retreatment, n/N (%)</th>
<th>High-Impact RAVs (&gt;5-fold Reduction in Susceptibility), n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>GT1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS3:</td>
<td>1/2 (50%)</td>
<td></td>
</tr>
<tr>
<td>NS5A:</td>
<td>0/2 (0%)</td>
<td></td>
</tr>
<tr>
<td>NS5B:</td>
<td>1/2 (50%)</td>
<td></td>
</tr>
<tr>
<td>GT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS3:</td>
<td>14/14 (100%)</td>
<td></td>
</tr>
<tr>
<td>NS5A:</td>
<td>13/14 (0%)</td>
<td>NS35A 31I/M: 11/14 (79%)</td>
</tr>
<tr>
<td>NS5B:</td>
<td>0/14 (0%)</td>
<td></td>
</tr>
<tr>
<td>GT3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS3:</td>
<td>8/8 (100%)</td>
<td>NS3 Q168R: 1/8 (13%)</td>
</tr>
<tr>
<td>NS5A:</td>
<td>7/8 (88%)</td>
<td>NS5A A30K: 3/8 (38%)</td>
</tr>
<tr>
<td>NS5B:</td>
<td>0/8 (0%)</td>
<td>NS5A L31M: 1/8 (13%)</td>
</tr>
<tr>
<td>NS35A 31I/M:</td>
<td>11/14 (79%)</td>
<td></td>
</tr>
<tr>
<td>NS5Q 168R:</td>
<td>1/8 (13%)</td>
<td></td>
</tr>
<tr>
<td>NS5A A30K:</td>
<td>3/8 (38%)</td>
<td></td>
</tr>
<tr>
<td>NS5A L31M:</td>
<td>1/8 (13%)</td>
<td></td>
</tr>
<tr>
<td>NS5A S62L:</td>
<td>2/8 (25%)</td>
<td></td>
</tr>
<tr>
<td>NS5A Y93H:</td>
<td>5/8 (63%)</td>
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</tr>
</tbody>
</table>

- 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

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

#### SVR12 (% Patients, 95% CI)

- GT1: 100 (2/2)
- GT2: 93 (13/14)
- GT3: 100 (8/8)

1 withdrew after single dose

#### Relapse
- GT1: 0
- GT2: 0
- GT3: 0

#### Discontinued
- GT1: 0
- GT2: 1
- GT3: 0
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