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High Sustained Virologic Response Rates at 24 Weeks in Participants With Chronic HCV GT1, 2, or 3 Infection Following 16 Weeks of Grazoprevir/Ruzasvir/Uprifosbuvir (MK-3682) Plus Ribavirin After Having Failed 8 Weeks of a Triple Drug Regimen (Part C of C-CREST-1 & 2)

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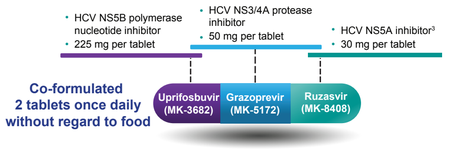
Background

- Combining 3 potent DAAs may provide effective treatment with shorter duration for most individuals, including those who failed prior all-oral DAA therapy

Objectives

Phase II C-CREST studies

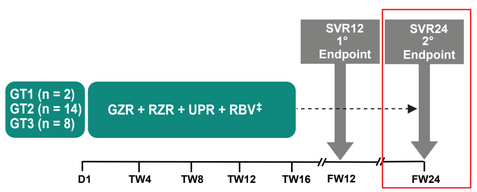
- **Part A:** Evaluate an NS3/4A inhibitor (grazoprevir, GZR), plus an NS5A inhibitor (either elbasvir, EBR, or ruzasvir, RZR) plus an NS5B inhibitor (uprifosbuvir, UPR; MK-3682)
  - Optimal regimen was GZR 100 mg/RZR 60 mg/UPR 450 mg once daily[1,2]
- **Part B:** Evaluated GZR/RZR/UPR +/- ribavirin (RBV) and durations in a wide population of HCV-infected persons
- **Part C:** Evaluate 16 weeks of GZR/RZR/UPR + RBV for individuals who failed 8 weeks in Part A



Methods

C-CREST Part C: study design

- Retreatment of participants who relapsed in Part A
  - Retreatment started 21-33 weeks after virologic failure in Part A
  - Weight-based RBV added‡
  - Duration of GZR + RZR + UPR + RBV was 16 weeks



‡RBV dose based on body weight (<65 kg=800 mg/d; 65-85 kg=1000 mg/d; >85-105 kg=1200 mg/d; >105 kg=1400 mg/d)
TW = treatment week; FW = follow-up week; RBV = ribavirin

- **Inclusion criteria**
  - Documented chronic HCV GT1, GT2, or GT3 infection
  - Relapse following 8 weeks of a 3-DAA regimen in Part A of this study
  - Non-cirrhotic, defined by one of the following:
    - Liver biopsy showing no cirrhosis (F0-F3) within 24 months
    - Fibroscan® ≤12.5 kPa within 12 months
    - Fibrosure® ≤0.48 AND AST/platelet ratio index (APRI) of ≤1 at screening

Methods (continued)

- **Exclusion criteria**
  - Co-infection with HBV
  - Significant laboratory abnormalities
    - ALT or AST ≥5 times ULN
    - Hemoglobin <11 g/dL in females or <12 g/dL in males
    - Platelets <125 x 10^3/μL

C-CREST Part C: endpoints

- **Primary efficacy endpoint**
  - SVR12, defined as HCV RNA <LLOQ [<15 IU/mL] 12 weeks after the end of treatment (EOT) (measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0)
- **Secondary efficacy endpoint:** SVR24 (HCV RNA <15 IU/mL at 24 weeks after EOT)
- **Resistance-associated substitutions (RAS) in NS3, NS5A, and NS5B**
  - Evaluated at time of initial failure and at retreatment baseline
  - Next-generation sequencing with 15% sensitivity threshold
    - **NS3 RASs:** Change from reference at 14 positions (36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, 175)
    - **NS5A RASs:**
      GT1 – Change from reference at 4 positions (28, 30, 31, 93)
      GT2 – Change from reference at 9 positions (24, 28, 30, 31, 32, 38, 58, 92, 93)
      GT3 – Change from reference at 10 positions (24, 28, 30, 31, 32, 38, 58, 62, 92, 93)
    - **NS5B RASs:** Change from reference at 6 positions (159, 239, 282, 316, 320, 321)

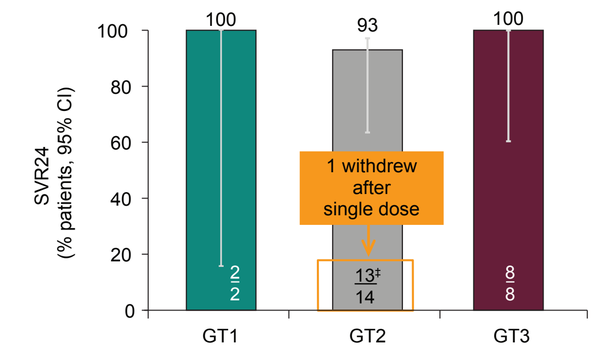
Results

C-CREST Part C: participant characteristics

	N = 24
Male, n (%)	12 (50)
Age, median years (range)	53 (28 to 75)
Race, white, n (%)	21 (88)
Metavir F0 to F2, n (%)	23 (96)
Body mass index ≥30 kg/m^2, n (%)	3 (13)
Retreatment baseline HCV RNA >2 million IU/mL, n (%)	17 (71)
Median baseline HCV RNA (log_{10} IU/mL)	6.6
HCV GT (subtype), n	2 GT1 (1 GT1a, 1 GT1b) 14 GT2 (8 GT2a, 4 GT2b, 2 GT2c) 8 GT3 (7 GT3a, 1 GT3b)
NS5A inhibitor in Part A regimen, GT (n) EBR RZR	 GT2 (9), GT3 (5) GT1 (2), GT2 (5), GT3 (3)
RASs at retreatment baseline, n (%) NS3 NS5A NS5B	 23 (96) 20 (83) 1 (4)

Results (continued)

SVR24 (full analysis set†)



	GT1	GT2	GT3
Relapse	0	0	0
Discontinued	0	1	0

†Full Analysis Set includes all participants who received ≥1 dose of study drugs.
‡One GT2 participant withdrew after a single dose with SAEs of vomiting and tachycardia.

Baseline RASs in Part A participants who enrolled in Part C retreatment

		At Part C Retreatment Baseline		
GT	Part A Regimen (8 weeks)	NS5A	NS3	NS5B
1a	GZR + RZR + UPR (450 mg/d)	WT	WT	WT
1b	GZR + RZR + UPR (450 mg/d)	WT	Y56F, V170I	C316N
2b	GZR + RZR + UPR (450 mg/d)	T24S, F28L, L31M	K122R, I132L	WT
2a	GZR + RZR + UPR (300 mg/d)	L31M, P58S	I132L	WT
2a	GZR + RZR + UPR (300 mg/d)	L31M	I132L	WT
2c	GZR + RZR + UPR (300 mg/d)	T24S, F28C, L31M	Y56F, K122R, I132L	WT
2a	GZR + RZR + UPR (300 mg/d)	L31I	I132L	WT
2b	GZR + EBR + UPR (450 mg/d)	T24S, F28L	K122R, I132L	WT
2a	GZR + EBR + UPR (450 mg/d)	L31M	I132L	WT
2a	GZR + EBR + UPR (450 mg/d)	T24S, L31M	I132L	WT
2a	GZR + EBR + UPR (450 mg/d)	L31M, P58S	I132L	WT
2a	GZR + EBR + UPR (450 mg/d)	T24A, L31M	Y56F, I132L	WT
2b	GZR + EBR + UPR (450 mg/d)	T24S, F28L, L31M	Y56F, K122R, I132L	WT
2a	GZR + EBR + UPR (300 mg/d)	WT	I132L	WT
2b	GZR + EBR + UPR (300 mg/d)†	T24S, F28L, L31M	K122R, I132L	WT
2c	GZR + EBR + UPR (300 mg/d)	T24S, F28C	Y56F, K122R, I132L	WT
3a	GZR + RZR + UPR (450 mg/d)	S62L, Y93H	V170I	WT
3b	GZR + RZR + UPR (450 mg/d)	A30K, L31M, S62D	V170I‡	WT
3a	GZR + RZR + UPR (300 mg/d)	A30K, S62T, Y93H	V170I	WT
3a	GZR + EBR + UPR (450 mg/d)	Y93H	L132I, V170I	WT
3a	GZR + EBR + UPR (450 mg/d)	WT	V170I	WT
3a	GZR + EBR + UPR (450 mg/d)	S62T, Y93H	Q168R, V170I	WT
3a	GZR + EBR + UPR (300 mg/d)	S62L, Y93H	V170I	WT
3a	GZR + EBR + UPR (300 mg/d)	A30K, S62P	V170I	WT

GZR = grazoprevir; RZR = ruzasvir; UPR = uprifosbuvir. †Participant did not complete retreatment due to withdrawal after SAE.
‡Sequence not available at retreatment baseline; V170I at Part A failure presumed unchanged.

C-CREST Part C: RASs present at retreatment

- The resistance analysis population included all 23 participants who had viral sequencing at baseline and a treatment outcome of either SVR12 or virologic failure
  - Resistance analyses excluded one GT2-infected participant who withdrew after a single dose due to vomiting and tachycardia
- All RASs observed at time of failure in Part A were also detected at initiation of retreatment in Part C
- 83% (19/23) of all participants had RASs in both NS3 and NS5A
- High-impact NS5A RASs (>5-fold reduction in susceptibility to RZR *in vitro*) were detected in:
  - 10/13 (77%) of GT2-infected participants
    - 9/13 (69%) had L31M; 2/13 (15%) had F28C; one participant had both
  - 7/8 (88%) of GT3-infected participants
    - 5/8 (63%) had Y93H, two of whom emerged at time of virologic failure in Part A
    - 3/8 (38%) had one (A30K or Y93H), 4/8 (50%) had two (A30K, L31M, S62L, or Y93H)
- No high-impact RASs were detected among GT1-infected participants

C-CREST Part C: laboratory abnormalities

Event, n (%)	N = 24
Hemoglobin <10 g/dL, n (%)	2 (8)
Direct bilirubin >5X baseline, n (%)	0
Late ALT/AST >5X ULN†, n (%)	0
Creatinine grade 1 (1.1–1.3X ULN), n (%)	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal;
†No ≥grade 2 ALT/AST elevations.

C-CREST Part C: adverse events

Event, n (%)	N = 24
One or more adverse event, n (%)	20 (83)
Treatment-related adverse event, n (%)	17 (71)
Serious adverse event, n (%)	2 (8)†
Treatment-related SAE, n (%)	1 (4)†
Death, n (%)	0
Treatment discontinuation due to AE, n (%)	2 (8)‡
AEs occurring in ≥20% of patients	
Headache	9 (38)
Fatigue	6 (25)
Nausea	6 (25)
Rash	5 (21)
Insomnia	5 (21)

Adverse events (AE) on treatment through 14 days of follow-up.
†Two participants had 3 SAEs: One GT2-infected participant withdrew after a single dose with SAEs of vomiting and tachycardia, considered related to GZR+RZR+UPR+RBV. One GT3-infected participant was hospitalized for severe anxiety, considered unrelated to GZR+RZR+UPR+RBV.
‡Two participants discontinued study drug: One GT2-infected participant withdrew after a single dose with SAEs as above.
One GT2-infected participant discontinued RBV 4 days before the scheduled completion of 16 weeks of therapy due to an AE of rash, considered RBV-related. This participant completed 16 weeks of GZR+RZR+UPR+RBV.

Summary

- Grazoprevir (GZR)/ruzasvir (RZR)/uprifosbuvir (UPR) plus RBV for 16 weeks was highly effective in HCV GT1-, 2-, and 3-infected participants without cirrhosis who had previously failed 8 weeks of treatment with a 3-DAA regimen, with 100% SVR24 in 23 patients who completed treatment
- GZR/RZR/UPR + RBV was highly effective despite a high prevalence of high-impact NS3 and NS5A RASs in this DAA-failure population
- Treatment was generally well tolerated
  - AE profile was consistent with other RBV-containing regimens

Conclusions

- Treatment with GZR/RZR/UPR + RBV for 16 weeks was well tolerated and highly effective in participants with HCV infection who had previously failed NS5A inhibitor-containing therapy
- Lack of impact of baseline RASs on the efficacy of 16 weeks of GZR/RZR/UPR + RBV demonstrates this regimen's high barrier to resistance
- These data support further investigation of this regimen in DAA treatment-experienced persons

References

1. Gane EJ et al. EASL, abstract SAT-139, 2016.
2. Gane EJ et al. AASLD, abstract LB-15, 2015.
3. Tong L, Yu W, Chen L, et al. *J Med Chem*. 2017;60(1):290-306.

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