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Efficacy and Safety of the Fixed-Dose Combination Regimen of Grazoprevir/Ruzasvir/Uprifosbuvir (MK-3682) With or Without Ribavirin in Non-cirrhotic or Cirrhotic Participants With Chronic HCV GT1, 2, 3, 4, or 6 Infection (Parts A & B of C-CREST-1 & 2)

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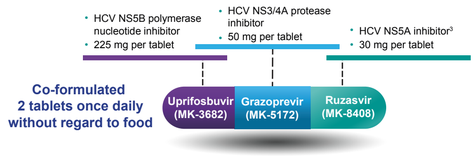
Background

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

Objectives

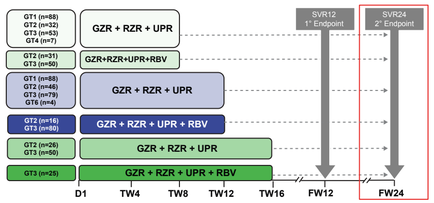
Phase II C-CREST studies

- **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
- **Part C:** Evaluate 16 weeks of GZR/RZR/UPR + RBV for participants who failed 8 weeks in Part A



Methods

C-CREST design (grazoprevir/ruzasvir/uprifosbuvir; N=675)



GT = genotype; TW = treatment week; FW = follow-up week; SVR = sustained virologic response.

- **Key inclusion criteria**
  - Documented chronic HCV GT1, GT2, GT3, GT4, or GT6 infection
  - GT1/2/4/6: Treatment-naïve; GT3: Treatment-naïve or prior peg-IFN/RBV failures
  - HCV RNA ≥10,000 IU/mL
  - HCV mono-infected or HIV/HCV co-infected
  - Cirrhotic or non-cirrhotic; cirrhosis defined by:
    - Liver biopsy prior to Day 1 showing cirrhosis (F4)
    - Fibroscan® within 12 months, with a result of >12.5 kPa
    - A Fibrosure® (Fibrotest®) score of >0.75 and AST/platelet ratio index (APRI) >2
- **Key exclusion criteria**
  - Decompensated liver disease (eg, Child-Pugh Class B or C)
  - Co-infection with HBV
  - Evidence or suspicion of hepatocellular carcinoma (HCC)
  - 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 (no cirrhosis), <75 x 10^3/µL (cirrhosis)
- **Endpoints**
  - Primary endpoint = SVR12, defined as HCV RNA <LLOQ [<15 IU/mL] 12 weeks after the end of treatment (EOT)
  - Secondary endpoint = SVR24; HCV RNA <15 IU/mL 24 weeks after EOT
  - HCV-RNA levels in plasma were measured using the Roche COBAS® AmpliPrep/ COBAS® TaqMan® HCV Test, v2.0
    - The presence of resistance-associated substitutions (RASs) in NS3, NS5A, and NS5B was evaluated at baseline (Day 1), at virologic failure, and during follow-up in those with failure
    - Next-generation sequencing (NGS) was performed with a 15% sensitivity threshold
- **Populations**
  - Full analysis set (FAS): All participants who received at least one dose of study drug
  - Per protocol: Excludes participants who failed for administrative reasons; includes participants who failed for drug-related adverse events; the single participant who had documented reinfection after clearance of baseline infection is counted as a success
  - Resistance analysis: Excludes participants who (a) discontinued for nonvirologic failure; and/or (b) have no baseline sequencing data

Results

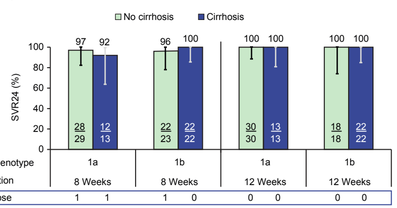
Demographics

	GT1, n=176	GT2, n=151	GT3, n=337	GT4, n=7	GT6, n=4	Overall GT1, GT2, GT3, GT4, GT6 (N=675)
Male, n (%)	107 (61)	86 (57)	199 (59)	6 (86)	2 (50)	400 (59)
Age, median years (range)	55 (19–81)	57 (25–85)	52 (19–77)	50 (30–58)	61 (43–63)	54 (19–85)
Race, White, n (%)	156 (89)	135 (89)	304 (90)	6 (86)	0 (0)	601 (89)
Black (or African American), n (%)	18 (10)	8 (5)	4 (1)	1 (14)	0 (0)	31 (5)
Ethnicity, Hispanic or Latino, n (%)	34 (19)	38 (25)	13 (4)	1 (14)	0 (0)	86 (13)
Cirrhosis (Metavir F4), n (%)	75 (43)	57 (38)	117 (35)	0 (0)	0 (0)	249 (37)
Body mass index, mean (range)†	27 (18–46)	27 (18–46)	27 (15–52)	25 (18–31)	25 (24–28)	26 (14–52)
Body mass index ≥30 kg/m², n (%)	43 (24)	36 (24)	77 (23)	1 (14)	0 (0)	157 (23)
Median baseline HCV RNA (log_{10} IU/mL)	6.2	6.4	6.3	5.7	6.5	6.3
HCV GT/subtype, n (%)						
GT1a	90 (51)	–	–	–	–	90 (13)
GT1b	86 (49)	–	–	–	–	86 (13)
Treatment-naïve, n (%)	176 (100)	151 (100)	189 (56)	7 (100)	4 (100)	527 (78)
Treatment (PR)-experienced, n (%)	–	–	148 (44)	–	–	148 (22)
HCV/HIV Co-infected, n (%)	10 (6)	5 (3)	12 (4)	1 (14)	0 (0)	28 (4)
Geographic region, n (%)						
North America	87 (49)	87 (58)	125 (37)	0 (0)	0 (0)	299 (45)
European Union	78 (44)	56 (37)	128 (38)	0 (0)	0 (0)	262 (39)
Asian Pacific	4 (2)	4 (3)	45 (13)	1 (14)	4 (100)	58 (9)
Middle East	7 (4)	4 (3)	39 (12)	6 (86)	0 (0)	56 (8)

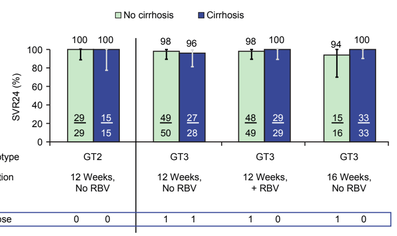
Note: Includes 614 treatment-naïve or peg-IFN/RBV treatment-experienced participants ± cirrhosis in Part B plus 61 treatment-naïve non-cirrhotic participants who received GZR/RZR/UPR (450 mg) in Part A.
†BMI results based on 173 GT1, 150 GT2, 337 GT3,7 GT4, 4 GT6 participants.

SVR24 (per protocol)

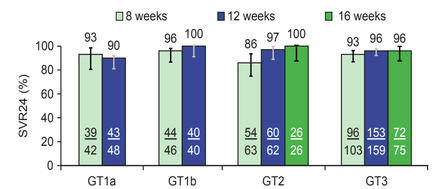
GT1 participants with or without cirrhosis



GT2 or GT3 participants with or without cirrhosis



SVR24 (Full Analysis Set) GT1–3: 8, 12, or 16 Weeks



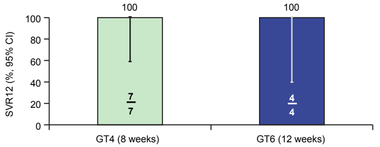
	GT1a		GT1b		GT2			GT3		
Relapse before FW12*	2	0	1	0	7	0	0	4	3	2
Discontinuation (DR-AE)	0	0	0	0	1	0	0	0	0	0
Reinfection	1	0	0	0	0	0	0	0	0	0
LTFU before FW12	0	1†	0	0	1	1	0	1	1	1
LTFU betw. FW12 & FW24	0	4	1	0	0	1	0	2	2	0

DR-AE = drug-related adverse event.
*There were no new virologic relapses between follow-up week 12 and follow-up week 24.
†1 participant died due to study-drug unrelated bacterial sepsis.

Efficacy Results for GT1, 2, and 3

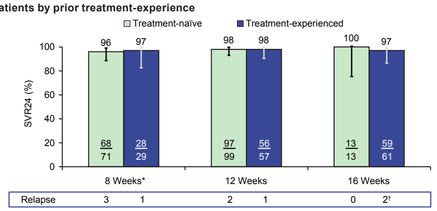
- At FW12, there were 19 participants who experienced virologic relapse and 8 participants who discontinued, were lost to follow-up, or reinfected
  - GT1a 8 weeks: 1 participant achieved SVR8 but was reinfected with a different HCV strain by phylogenetic analysis at FW12
  - GT1a 12 weeks: 1 participant died due to study-drug unrelated bacterial sepsis
  - GT2 8 weeks + RBV: 1 participant discontinued at Day 5 due to drug-related AEs of fatigue, malaise; 1 participant lost to follow-up (LTFU)
  - GT2 12 weeks, No RBV: 1 participant LTFU
  - GT3 8 weeks + RBV: 1 participant LTFU
  - GT3 12 weeks: 1 participant withdrew due to pregnancy, then was LTFU
  - GT3 16 weeks: 1 participant LTFU
- There were no new virologic relapses between FW12 and FW24
- There were additional participants who were lost to follow-up between FW12 and FW24
  - GT1b 8 weeks: 1 participant LTFU
  - GT1a 12 weeks: 4 participants LTFU
  - GT2 12 weeks: 1 participant LTFU
  - GT3 8 weeks: 2 participants LTFU
  - GT3 12 weeks + RBV: 1 participant had study-drug unrelated SAE of cerebral hemorrhage and was subsequently LTFU and 1 participant was LTFU

SVR12 (Full Analysis Set) in GT4 and GT6



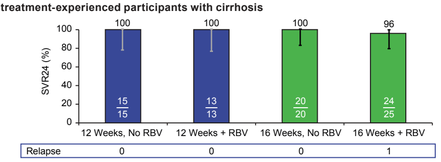
SVR24 (per protocol)

GT3 patients by prior treatment-experience



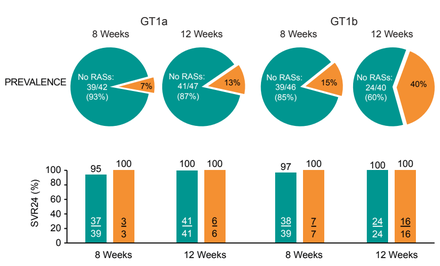
*8 week arm included only non-cirrhotic participants.
†One participant with cirrhosis relapsed.

GT3 treatment-experienced participants with cirrhosis

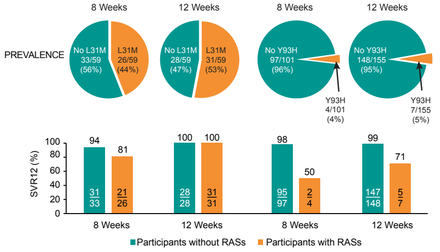


Selected NS5A RASs (28, 30, 31, 93)

Prevalence and Impact on Efficacy in GT1



Prevalence and Impact on Efficacy of L31M in GT2 and Y93H in GT3



Tolerability

	GZR + RZR + UPR Without RBV (n=473)	GZR + RZR + UPR With RBV (n=202)	Overall (N=675)
One or more AEs, n (%)	327 (69)	173 (86)	500 (74)
Drug-related AE, n (%)	167 (35)	135 (67)	302 (45)
Serious AE, n (%)	11 (2)	5 (2)	16 (2)
Drug-related serious AE, n (%)	0 (0)	2 (1)†	2 (0.3)
Death, n (%)	1 (0.2)‡	0 (0)	1 (0.2)
Discontinuation due to AE, n (%)	3 (0.6)	6 (3)§	9 (1)§
Hemoglobin <10 g/dL, n (%)	2 (0.4)	6 (3)	8 (1)
Total bilirubin >5 x baseline, n (%)	1 (0.2)	6 (3)	7 (1)
Late ALT/AST >5 x ULN, n (%)	6 (1)	0 (0)	6 (0.9)
Creatinine grade 1 (1.1–1.3 x ULN), n (%)	3 (0.6)	0 (0)	3 (0.4)
Creatinine grade 2 (1.4–1.8 x ULN), n (%)	1 (0.2)	1 (0.5)	2 (0.3)
Most common AEs (>10%), n (%)			
Headache	91 (19)	55 (27)	146 (22)
Fatigue	70 (15)	59 (29)	129 (19)
Nausea	52 (11)	31 (15)	83 (12)

†One GT3-infected participant had an exacerbation of chronic obstructive pulmonary disease related to RBV; one GT2-infected participant had a worsening of depression related to RBV.
‡One GT1-infected participant died due to a study drug-unrelated bacterial sepsis.
§Four participants discontinued RBV only.

Summary

- Grazoprevir (GZR) + ruzasvir (RZR) + uprifosbuvir (UPR) without ribavirin (RBV) for 8 or 12 weeks was highly effective in GT1 participants
- GZR + RZR + UPR for 12 or 16 weeks without RBV was highly effective in GT2 participants
- GZR + RZR + UPR for 12 or 16 weeks without RBV was highly effective in GT3 treatment-naïve or treatment-experienced participants
  - Efficacy was maintained in GT3 treatment-experienced participants with cirrhosis
  - 8 weeks of treatment was highly effective in GT3 treatment-naïve non-cirrhotic participants
- There were no new virologic relapses between FW12 and FW24 for GT1, 2, or 3
- 100% (7/7) of GT4 participants treated with 8 weeks of GZR + RZR + UPR achieved SVR12
- 100% (4/4) of GT6 participants treated with 12 weeks of GZR + RZR + UPR achieved SVR12
- GZR + RZR + UPR was generally well-tolerated

Conclusions

- A 12-week regimen with GZR + RZR + UPR without RBV was a highly effective and well-tolerated regimen for the treatment of HCV infection, including high efficacy in GT3-infected cirrhotic participants who were peg-IFN/RBV treatment-experienced
- These data support further investigation of GZR + RZR + UPR

References

1. Gane EJ, et al. EASL. Abstract SAT-139. 2016.
2. Gane EJ, et al. AASLD. Abstract LB-15. 2015.
3. Tong et al. *J Med Chem*. 2017;60:290.

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