INTERFERON-FREE TREATMENT WITH A COMBINATION OF MERICITABINE AND DANOPREVIR/R WITH OR WITHOUT RIBAVIRIN IN TREATMENT-NAIVE HCV GENOTYPE 1-INFECTED PATIENTS

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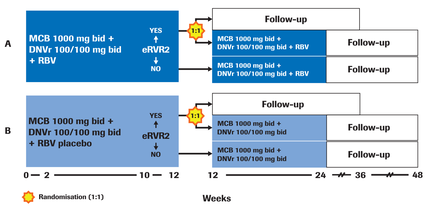
INTRODUCTION

- The hepatitis C treatment landscape is rapidly evolving. The recent regulatory approval of first-generation protease inhibitors has resulted in a new standard of care for genotype 1 patients, consisting of peginterferon alfa/ribavirin (RBV) in combination with telaprevir or boceprevir, with sustained virological response (SVR) rates of 68–75% achievable in treatment-naive patients.[1-3]
- However, safety and tolerability remain suboptimal. The benefits of adding one direct-acting antiviral agent (DAA) to peginterferon alfa/RBV remain limited due to the underlying safety and tolerability issues associated with interferon-based treatment.
- An all-oral, interferon-free DAA combination treatment would fill an unmet medical need and potentially further change the treatment paradigm.[4]
- Two DAAs currently in phase II clinical development are mericitabine (MCB) and danoprevir (DNV; RG7227).
- MCB is a selective and non-cytotoxic hepatitis C virus (HCV) polymerase inhibitor which is active against all HCV genotypes and has a high barrier to resistance.[5-7]
- DNV is a potent, macrocyclic, HCV protease inhibitor that has equipotent activity against HCV genotypes 1, 4 and 6 in vitro.[8,9]
- The phase I INFORM-1 study demonstrated that treatment with a combination of these two DAAs for 13 days resulted in significant reductions in HCV RNA in both treatment-naive and prior null responders and was well tolerated.[4]
- Co-administration of ritonavir with lower doses of DNV has since been shown to decrease the overall exposure of DNV while maintaining potent antiviral activity.[10]
- The phase IIb INFORM-SVR study is investigating the safety and efficacy of response-guided treatment with MCB in combination with ritonavir-boosted DNV (DNVr) with and without RBV for 12 or 24 weeks in treatment-naive patients with genotype (G) 1 chronic HCV infection.
- Here, results from a 12-week post-treatment interim analysis of the INFORM-SVR study are presented.

METHODS

- INFORM-SVR is an ongoing, randomised, multicentre, double blind, parallel group phase IIb study.
- Eligible patients are treatment-naive, chronic HCV G1-infected adults (≥18 years of age) with F0–F2 fibrosis.
- Patients were randomised (1:1) to receive a combination of MCB (1000 mg bid) and DNVr (100 mg/100 mg bid) plus either RBV (1000/1200 mg daily) (Arm A) or placebo (Arm B) for 12 or 24 weeks (**Figure 1**).
- In both arms, patients achieving an early extended rapid virological response (eRVR2, defined as unquantifiable HCV RNA [<43 IU/mL]) between week 2 to week 8, and with undetectable HCV RNA [<15 IU/mL] at week 10, were re-randomised (1:1) at week 12 to either discontinue treatment (total therapy duration: 12 weeks) or continue the assigned regimen until week 24 (total therapy duration: 24 weeks).
- HCV RNA was measured using Roche COBAS® AmpliPrep/COBAS TaqMan® HCV Test with a lower limit of detection of 15 IU/mL and a lower limit of quantification of 43 IU/mL.
- The primary outcome of the trial was SVR24.
- Resistance monitoring was performed in patients who experienced breakthrough, partial response, non-response or relapse through sequencing (population and clonal) of target genes.

Figure 1: INFORM-SVR study design



Arm A (12 week option) and Arm B (both 12 and 24 week options) stopped prematurely at different times due to unexpectedly high relapse rates.

eRVR2: extended rapid virologic response; HCV RNA unquantifiable (<43 IU/mL) between week 2 and 8 and undetectable (<15 IU/ml) at week 10. Continue if HCV RNA quantifiable between week 2 and week 8 (≥43 IU/mL) but <43 IU/mL at week 10, or, HCV RNA <43 IU/mL between week 2 and 8 and <43 IU/mL but ≥15 IU/mL at week 10. Patients with virologic failure (confirmed rebound or <2 log drop after 1 month of treatment) discontinued treatment. Patients with quantifiable virus at week 10 stopped treatment at week 12.

RESULTS

Patients

- A total of 169 patients were randomised to treatment (Arm A n=83; Arm B n=86) and received at least one dose of study medication.
- Demographics were balanced between arms (**Table 1**).

Table 1: Baseline characteristics of the study population

		MCB + DNVr + RBV (n=83)	MCB + DNVr + placebo (n=86)
Male, n (%)		46 (55)	43 (50)
Race, n (%)	White	72 (87)	75 (87)
Mean age, years		50.7	49.5
Mean weight, kg		77.9	77.3
Mean BMI, kg/m^2		26.7	26.2
HCV genotype, n (%)	1a	56 (67)	57 (66)
	1b	27 (33)	29 (34)
Mean HCV RNA, $\log_{10}$ IU/mL		6.52	6.35
ALT, U/L		90	89
Host *IL28B* genotype, n (%)	CC	26 (31%)	26 (30%)
	Non-CC	57 (69%)	60 (70%)

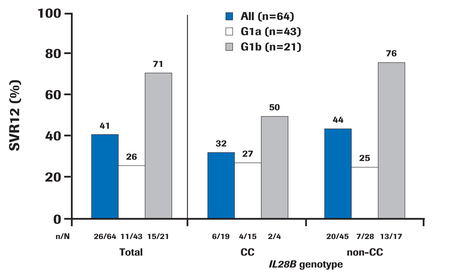
ALT = alanine aminotransferase; BMI = body mass index; DNVr = ritonavir-boosted danoprevir; MCB = mericitabine; RBV = ribavirin.

- Randomisation to 12 weeks of treatment in Arm A and to the whole of Arm B was stopped prematurely due to high relapse rates, and patients in Arm B were offered follow-on with peginterferon alfa-2a (40KD)/RBV therapy.
- As a result, only 20/169 patients were randomised to 12 weeks of treatment (Arm A n=17; Arm B n=3) and thus, for efficacy analyses, Arm A (24 weeks of treatment), is the key group analysed here (n=66).

Efficacy

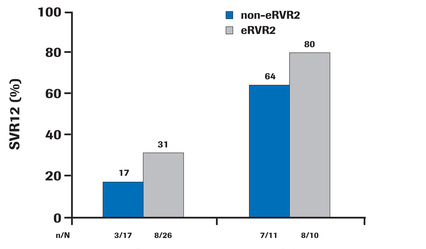
- Among patients randomised to Arm A for 24 weeks (n=66), two patients were excluded from the present efficacy analysis; one patient discontinued for reasons other than virological breakthrough or an adverse event (AE) and one patient was lost to follow-up.
- The efficacy population thus consisted of 64 patients who received MCB combined with DNVr and RBV for 24 weeks; 43 patients with HCV G1a and 21 with HCV G1b.
- SVR12 rates for G1a and G1b patients receiving 24 weeks of MCB plus DNVr and RBV treatment are presented in **Figure 2**.
  - Overall, 41% of patients achieved SVR12 (26/64; 95% CI 28–53). However, SVR12 rates were considerably higher among patients with HCV G1b (71%; 95% CI 50–92) compared with patients with G1a infection (26%; 95% CI 12–39)
  - When SVR12 rates were stratified according to *IL28B* genotype (CC and non-CC), 32% of patients with *IL28B* CC genotype, and 44% with non-CC genotype achieved SVR12
  - In G1a patients, SVR12 rates were similar irrespective of *IL28B* genotype. However, in G1b patients the number of *IL28B* CC patients was too small (n=4) to allow a meaningful comparison to patients with *IL28B* non-CC genotype.
- Among patients in Arm A treated with MCB combined with DNVr and RBV for 24 weeks, 60.5% (26/43) of HCV G1a-infected patients achieved an eRVR2 compared to 47.6% (10/21) of patients with HCV G1b infection.
- Among the patients achieving an eRVR2, 31% (8/26) of G1a and 80% (8/10) G1b achieved an SVR (**Figure 3**).

Figure 2: SVR12 rates in patients receiving 24 weeks MCB + DNVr + RBV (Arm A) by HCV genotype and *IL28B* genotype



G = HCV genotype; DNVr = ritonavir-boosted danoprevir; MCB = mericitabine; RBV = ribavirin; SVR12 = sustained virological response after 12 weeks of untreated follow-up.

Figure 3: SVR12 rates according to eRVR2 status and HCV genotype in patients randomised to MCB + DNVr + RBV for 24 weeks (Arm A)



G = HCV genotype; DNVr = ritonavir-boosted danoprevir; eRVR = extended rapid virological response; MCB = mericitabine; RBV = ribavirin; SVR12 = sustained virological response after 12 weeks of untreated follow-up.

Breakthrough rates

- In total, among all patients who received at least one dose of study medication, 26 patients experienced breakthrough: 8 in Arm A (8/83; 9.6%) and 18 in Arm B (18/86; 20.9%).
- When evaluated by HCV genotype, breakthrough rates were higher among HCV G1a patients (Arm A: 6/56; 11%; Arm B: 15/57; 26%) compared to G1b patients (Arm A: 2/27; 7%; Arm B: 3/29; 10%).
- DNV resistance mutations were detected by population sequencing in 25 patients at virological breakthrough; sequencing could not be performed in one G1a patient due to low viral load.
  - The NS3 R155K amino acid change was the only known DNV resistance mutation detected at the population level in 16 patients (14 G1a, two G1b)
  - R155K + V36M/A was observed in five G1a patients
  - D168T was observed in one G1b patient
  - D168E + V36V/G was observed in one G1b patient
  - One patient (GT1a) had a dual resistant virus to MCB and DNV, bearing substitutions NS5B S282T and NS3 R155K
  - R155K/Q was observed in one G1b-infected patient
- The dual resistant virus reverted to wild type by week 12 of follow-up (T282S at week 8 and K155R at week 12); clonal sequencing and/or ultra-deep pyrosequencing analyses are ongoing.

Safety

- Treatment with MCB in combination with DNVr and RBV was safe and well tolerated and no safety concerns were identified (**Tables 2 and 3**).
- No serious AEs were reported during treatment in Arm A.
- No Grade 4 laboratory abnormalities were reported (**Table 2**).

Table 2: Adverse events and laboratory abnormalities

Adverse Event	MCB + DNVr + RBV (n=83)
Patients with ≥ 1 AE, n (%)	81 (98%)
Number of AEs	567
Number of SAEs	1*
Deaths	0
Discontinuation from MCB/DNVr due to AE, n (%)	1†
Grade 3 laboratory abnormalities, n	
ALT/AST	0
Bilirubin	0
ANC	0
Haemoglobin	1
Triglycerides	0
Cholesterol	4
Phosphate	1
Lipase	1

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DNVr = ritonavir-boosted danoprevir; MCB = mericitabine; RBV = ribavirin.
* SAE due to multiple myeloma at 63 days after last dose
† discontinuation was due to oropharyngeal discomfort

Table 3. Most common adverse events (≥10%)*

Adverse Event	MCB + DNVr + RBV (n=83)
Headache	45%
Fatigue	42%
Nausea	29%
Diarrhoea	29%
Nasopharyngitis	17%
Insomnia	17%
Pruritus	16%
Asthenia	14%
Irritability	14%
Dizziness	14%
Dyspnoea	14%
Cough	14%
Arthralgia	13%
Dyspepsia	13%
Vomiting	11%
Rash	10%
Anxiety	10%
Back pain	10%

DNVr = ritonavir-boosted danoprevir; MCB = mericitabine; RBV = ribavirin.
* Includes mild, moderate and severe AEs

CONCLUSIONS

- In G1b patients, 24 weeks of MCB in combination with DNVr and RBV yielded an SVR12 rate of 71%, while in G1a patients the SVR12 rate was 26%.
- Higher SVR12 rates were reported among patients who were rapid responders, i.e. those who achieved an eRVR2. Among patients with an eRVR2, 80% with G1b and 31% with G1a achieved SVR12.
- *IL28B* genotype (CC and non-CC) appeared to have less impact on SVR12 rates relative to differences observed between HCV G1a and G1b patients.
- Among patients not receiving RBV, breakthrough rates were higher indicating that RBV still plays an important role in preventing viral breakthrough.
- All patients with a confirmed viral breakthrough showed DNV-resistant variants, while only one patient showed the NS5B S282T polymerase mutation associated with resistance to MCB.
- Combination of MCB, DNVr and RBV is safe and well tolerated, resulting in no significant cytopenias, no treatment-emergent alanine aminotransferase elevations or any new signals with combination therapy.
- In view of its promising efficacy in G1b patients (>70%) and its good tolerability and safety profile, this interferon-free regimen warrants further study.

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