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Safety and efficacy of ravidasvir plus sofosbuvir for 12 weeks in non-cirrhotic and 24 weeks in cirrhotic patients with hepatitis C virus genotypes 1, 2, 3 and 6: the STORM-C-1 phase II/III trial stage 1 results

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INTRODUCTION

By 2030, WHO aims to test 90% and treat 80% of people with hepatitis C virus infection (HCV) worldwide. Access to treatment is hindered by the very high prices of direct-acting antivirals (DAAs) and low level of political commitment to address the HCV epidemic. In low- and middle-income countries, affordable DAAs for a public health approach to HCV treatment are urgently needed. Ravidasvir, an oral NS5A inhibitor with pangenotypic potential, was developed by DND*i* and its partners as an affordable DAA for public health use. The combination of ravidasvir and sofosbuvir has shown excellent efficacy and safety in HCV patients with genotype 4 in Egypt (Esmat 2018).

AIM

The STORM-C-1 trial is an open label trial aiming to assess the efficacy, safety, tolerance and pharmacokinetics of sofosbuvir plus ravidasvir (SOF-RDV) in Malaysia and Thailand, where genotypes 1 and 3 are prevalent.

METHODS

Study design

Two-stage, open label, multicentre trial:

- 12 weeks SOF-RDV in patients with chronic HCV infection and no cirrhosis (Metavir F0 to F3)
- 24 weeks SOF-RDV in patients with compensated cirrhosis (Metavir F4 and Child-Turcotte-Pugh class A)

We report here the results of the stage 1 trial.

Stage 1 analysis strategy

Based on published results for other treatments, we considered that the overall SVR12 rate should be >85% in the ITT analysis. A sample size of 300 patients provides over 86% power to detect at least 6% improvement in the overall SVR12 rate from this pre-specified performance goal of 85% (two-sided exact binomial test, alpha=0.05).

Efficacy analysis populations

Intent to treat (ITT)	Per protocol
Patients who: • Did not report active injection drug use at eligibility visit • Received at least one dose of a study drug	Patients in the ITT population who: • Did not prematurely discontinue the study • Had an adherence to SOF+RDV ≥ 90% • Did not have missing SVR12 results • Had no major protocol deviation during the study

Primary endpoint: sustained virologic response at 12 weeks post-treatment (SVR12)

RESULTS

POPULATION BASELINE CHARACTERISTICS

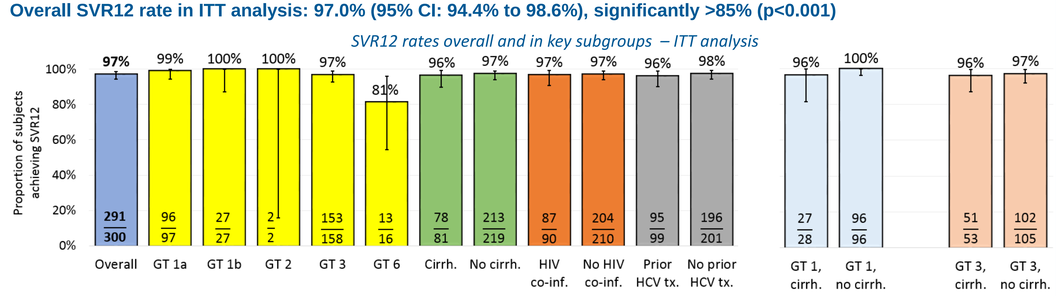
300 patients enrolled between October 2016 and June 2017 were included in the intention-to-treat (ITT) analysis:

Sex	Age	Genotype	Compensated cirrhosis (CPT A)	HCV RNA ≥800,000 IU/mL	HIV co-infection	Prior interferon experience	History of injection drug use	On methadone
Male: 230 (70%) Female: 70 (30%)	Median 47 years (IQR 40 to 56)	1a: 97 (32%) 1b: 27 (9%) 2: 2 (1%) 3: 158 (53%) 6: 16 (5%)	Yes: 81 (27%) No: 219 (73%)	Yes: 216 (72%) No: 84 (28%)	Yes: 90 (30%) No: 210 (70%)	Yes: 99 (33%) No: 201 (67%)	Yes: 133 (44%) No: 167 (56%)	Yes: 25 (8%) No: 275 (92%)

RATES OF SUSTAINED VIROLOGIC RESPONSE AT 12 WEEKS POST-TREATMENT (SVR12)

Overall SVR12 rate in ITT analysis: 97.0% (95% CI: 94.4% to 98.6%), significantly >85% (p<0.001)

SVR12 rates overall and in key subgroups – ITT analysis



Overall SVR12 rate in per protocol analysis: 98.3% (95% CI: 96.1% to 99.4%), 288/293 patients

FAILURES AT WEEK 12 POST-TREATMENT

Failure type	GT	Cirrh.	HIV co-inf.	Prior HCV tx.	RASs at baseline & failure	Details
Breakthrough	3	Yes	No	Yes	30T-93H	Breakthrough at Week 20
Relapse	6	No	No	Yes	93S	Relapse at Week 4 post-treatment
Relapse	6	No	No	No	Pending	Relapse at Week 4 post-treatment
Relapse	3	No	No	No	93H	Relapse at Week 12 post-treatment
Relapse	6	No	Yes	No	Pending	Relapse at Week 12 post-treatment
Non-virologic	3	No	Yes	No	-	Discontinued treatment on Day 1 due to AEs (fatigue, diarrhea and abdominal discomfort)
Non-virologic	1a	Yes	Yes	Yes	-	Discontinued treatment on Day 2 due to AEs (vomiting, palpitation and prolonged QT)
Non-virologic	3	No	No	Yes	-	Discontinued treatment on Day 4 due to possible complications that may arise from treatment
Non-virologic	3	Yes	No	No	-	Discontinued treatment on Day 9 due to AEs (tiredness, palpitations, hot flush and breast engorgement)

ADVERSE EVENTS

629 adverse events (AEs) were reported in 192/300 (64%) patients.

Severity:

Mild	Moderate	Severe	Life-threatening	Death
450 (72%)	126 (20%)	52 (8%)	1 (<1%)	0 (0%)

Most frequent AEs: pyrexia (n=45, 7%); cough (n=35, 6%); upper respiratory tract infection (n=29, 5%); and headache (n=24, 4%).

29 serious adverse events (SAEs) were reported, of which one transient acute renal failure in a HIV-HCV co-infected patient and one syncope of unknown origin were possibly related to study drugs.

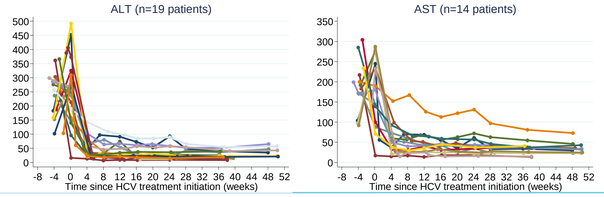
ELECTROCARDIOGRAPHY

There was one prolonged QTc, one episode of palpitations, and one sinus bradycardia with prolonged QTc at week 12 post-treatment possibly related to study drugs.

LABORATORY ABNORMALITIES

Number of patients with…	At baseline	While on treatment	After treatment
ALT ≥ 5.0 x ULN	19	0	1
AST ≥ 5.0 x ULN	14	0	1
Total bilirubin ≥ 2.6 x ULN	3	2	2
ALT ≥ 3.0 x ULN and total bilirubin ≥ 2.0 x ULN	3	0	0
Serum creatinine ≥ 1.8 x ULN	1	2	0

ALT or AST ≥ 5.0 x ULN at baseline: change over time



PHARMACOKINETIC INTERACTIONS WITH ANTIRETROVIRALS

No clinically significant drug interactions were observed between ravidasvir and the usual HIV antiretroviral drugs (Cressey, CROI 2018).

CONCLUSIONS

- With 12 weeks of treatment in non-cirrhotic and 24 weeks in cirrhotic patients, sofosbuvir plus ravidasvir was highly effective, regardless of HCV genotype, HIV infection and previous interferon experience. Treatment was well tolerated in all subgroups.
- Stage 2 of this study is under preparation. Further studies are being designed to ensure good representation of all key subgroups, in particular those with genotype 6, as well as key populations (people who inject drugs, people with advanced liver disease, people co-infected with HIV).

REFERENCES

- WHO. Hepatitis C Fact Sheet. Updated Oct. 2107. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/
- Esmat G, et al. Effectiveness of ravidasvir plus sofosbuvir in interferon-naïve and treated patients with chronic hepatitis C genotype-4. *J Hepatol*. 2018; 68(1): 53-62.
- Cressey TR, et al. Ravidasvir pharmacokinetics and ARV drugs interactions in HCV+/-HIV infected adults. CROI 2018, poster.
- Andrieux-Meyer I, et al. Tolérance et efficacité du ravidasvir-sofosbuvir pendant 12 semaines chez des patients non cirrhotiques et 24 semaines chez des patients cirrhotiques co-infectés VIH-hépatite C avec génotype 1, 2, 3 ou 6 dans l'essai STORMC-1. AFRAVIH 2018, oral presentation.

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