SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL PP25213)

COMPANY: F. Hoffman – La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): Mericitabine (RO5024048)	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Final Clinical Study Report – Protocol PP25213 – INFORM-SVR: A Randomized, Multi-Center Study of Interferon-Free Treatment with a Combination of a Polymerase Inhibitor (RO5024048) and a Ritonavir boosted HCV Protease Inhibitor (RO5190591/r, DNV/r) with or without Copegus® in Interferon Naïve HCV Genotype 1 Infected Patients – Report No. [redacted]. August 2013.
INVESTIGATORS / CENTERS AND COUNTRIES	29 centers in 4 countries: France (6), Germany (7), USA (15), and New Zealand (1)
PUBLICATION (REFERENCE)	Gane EJ, Pockros P, Zeuzem S, et al. Interferon-free treatment with a combination of mericitabine and danoprevir/r with or without ribavirin in treatment-naïve HCV genotype 1-infected patients [poster]. Presented at: The 47th Annual Meeting of the European Association for the Study of the Liver (EASL), April 18-22, 2012. Barcelona, Spain.
PERIOD OF TRIAL	First Patient Entered: 24 February 2010 Last Patient Last Visit: 16 October 2012
CLINICAL PHASE	2b
OBJECTIVES	**Primary:** To establish the safety, tolerability and efficacy (sustained virologic response at 24 weeks post treatment [SVR24]) of up to 24 weeks of treatment with interferon (IFN)-free regimen of RO5024048 (mericitabine [MCB]) and danoprevir/ritonavir (DNV/r), with or without ribavirin (RBV) in IFN-naïve chronic hepatitis C (CHC) genotype 1 patients. **Secondary:** • To establish the antiviral activity (rapid virologic response [RVR], end of treatment [EOT], SVR at 12 weeks post treatment [SVR12]) of up to 24 weeks of treatment with an IFN-free regimen of RO5024048 and DNV/r, with or without RBV • To determine the impact of RBV on safety, tolerability and antiviral activity of the direct acting antiviral (DAA) combination regimen • To compare 12 or 24 weeks duration on safety, tolerability and antiviral activity of the DAA combination regimens • To evaluate the pharmacokinetics/pharmacodynamics of RO5024048, DNV/r and RBV when co-administered

	• To characterize drug resistance when RO5024048 and DNV/r are co-administered in the presence or absence of RBV • To assess the effect of IL28b genotype on treatment efficacy • To assess the effect of IFN-free treatment on patient reported quality of life measures
STUDY DESIGN	Randomized, blinded, placebo controlled, study comparing a combination of MCB and DNV/r either with RBV (Arm A) or placebo (Arm B) in hepatitis C virus (HCV) genotype 1-infected, IFN naïve adult patients. Randomization was stratified by viral genotype (1a and 1b) and IL28B polymorphism (CC and non-CC). The study consisted of the Main Protocol (evaluation between Arm A and Arm B) and peginterferon alfa-2a (PEG-IFN)/RBV Extension (in which Arm B patients received open-label PEG-IFN and RBV). All patients, including patients in the PEG-IFN/RBV Extension, were followed for up to 24 weeks after stopping study treatment. Details are provided below (see “Methodology”).
NUMBER OF SUBJECTS	Approximately 160 patients (80 per treatment arm) were planned for the Main Protocol. 170 patients were randomized: 84 patients to Arm A and 86 patients to Arm B. A total of 44 patients from Arm B entered the PEG-IFN/RBV Extension.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Males and females ≥18 years of age with chronic HCV genotype 1 infection and HCV RNA ≥50,000 IU/mL who never previously received treatment with IFN. Patients with cirrhosis, incomplete/transition to cirrhosis, or other forms of liver disease were excluded.
TRIAL DRUG / STROKE (BATCH) No.	MCB: [redacted] DNV: [redacted] Ritonavir (RTV): [redacted] PEG-IFN: [redacted] RBV: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	MCB: 500 mg tablet, 1000 mg BID / oral / up to 24 weeks DNV: 100 mg tablet, 100 mg BID / oral / up to 24 weeks RTV: 100 mg tablet, 100 mg BID / oral / up to 24 weeks PEG-IFN: 180 μg/mL sc injection QD / up to 24 weeks RBV: 1000 mg (<75 kg) or 1200 mg (≥75 kg) as 200 mg tablets administered orally twice daily for up to 24 weeks
REFERENCE DRUG / STROKE (BATCH) No.	RBV Placebo: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	1000 mg (<75 kg) or 1200 mg (≥75 kg) as 200 mg tablets administered orally twice daily for up to 24 weeks
CRITERIA FOR EVALUATION	

EFFICACY:	**Primary:** SVR24, defined as the proportion of patients with undetectable HCV RNA at 24 weeks after end of treatment (a single last HCV RNA undetectable $\geq$20 weeks after last dose of study medication) **Secondary:** Virologic response (percentage of patients with undetectable HCV RNA at last dose of study treatment); SVR12 (percentage of patients with undetectable HCV RNA at 12 weeks after last dose of study treatment); relapse rate (percentage of patients with virologic response at end of treatment but who had quantifiable HCV RNA at last assessment post-treatment)
PHARMACODYNAMICS:	Blood samples were collected to assess viral kinetic response and emergence of resistance. Phenotypic and sequence analyses were performed in patients who experienced HCV RNA breakthrough, partial response, or non-response, and in patients who relapsed.
PHARMACOKINETICS:	Blood samples were collected to evaluate the PK of RO4995855, DNV, RTV and RBV.
SAFETY:	Adverse events (AEs), serious AEs (SAEs), safety laboratory tests, physical examination, vital signs, and electrocardiograms
STATISTICAL METHODS:	Mean, standard deviation, standard error, median, minimum and maximum values for continuous variables. Number and percentage for categorical variables. The 95% CIs for virologic response rates and relapse rates were calculated using the Wilson formula.

METHODOLOGY

An abbreviated report of this study is provided instead of a full report because the dual IFN-free combination therapy of MCB and DNV/r is no longer under investigation as a treatment for CHC.

Main Protocol: During Weeks 0-12, patients were randomized to receive MCB and DNV/r with either RBV (Arm A) or placebo (Arm B). During Weeks 12-24, patients were treated based on their virologic response between Week 2 and Week 10; treatment options included discontinuing treatment at Week 12 or continuing treatment until Week 24. In both treatment arms, due to high viral relapse rates observed in patients who discontinued treatment at Week 12, it was decided to allow all patients to continue their originally assigned treatment regimen until Week 24. Thus, in both treatment arms, there were patients who received treatment up to 12 weeks (Group A12/RBV; Group B12/Placebo) and patients who received treatment up to 24 weeks (Group A24/RBV; Group B12/Placebo).

PEG-IFN/RBV Extension (Arm B):During study conduct, due to a higher than expected relapse rate in Arm B, open-label PEG-IFN/RBV for 24 weeks was offered to patients in Arm B. Patients took PEG-IFN/RBV concomitantly with MCB + DNV/r until 24 weeks of dosing with MCB + DNV/r was completed. Subsequently, patients remained on the PEG-IFN/RBV combination up to a total duration of 24 weeks.

EFFICACY RESULTS

The efficacy of the IFN-free combination regimen of MCB and DNV/r, with or without RBV, was not established irrespective of treatment duration. In Group A12/RBV, 3 patients (17.6% [95% CI: 6.2, 41.0%]) achieved SVR24. In Group A24/RBV, 25 of 66 patients (37.9% [95% CI: 27.1, 49.9%]) achieved SVR24. In Arm B, only 2 of 86 patients (2.3%) achieved SVR24.

HCV genotype subgroup analysis performed in Arm A patients showed higher SVR24 in genotype 1b-infected patients than in genotype 1a-infected patients (16 of 27 patients [59.2%] and 12 of 56 patients [21.4%], respectively). No clear impact of IL28B haplotype was observed. The majority of treatment failures was associated with virologic relapse. Population sequencing at the time of relapse identified mutations associated with DNV resistance in 97 of 98 evaluable patients, suggesting that drug resistance contributes to treatment failure.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS

Overall, DNV and RO4995855 exposures were within the range of those previously reported.

Viral kinetics were monitored for 169 patients who received study treatment. Of 102 patients who failed to achieve SVR, 30 patients (including 20 genotype 1a and 6 genotype 1b) had detectable HCV RNA ($>$15 IU/mL) at the end of study treatment, 63 patients (48 genotype 1a, 15 genotype 1b) experienced relapse after the end of study treatment, 4 patients (3 genotype 1a, 1 genotype 1b) discontinued treatment early due to reasons unrelated to virologic response and 5 patients experienced virologic failure after receiving PEG-IFN/RBV Extension treatment.

Known mutations associated with protease inhibitor resistance were observed in baseline NS3 sequences from 7 patients. No pre-existing MCB resistance mutation S282T or L159+L320F was found in any of the baseline NS5B sequences. NS3 population sequencing detected DNV resistance mutations in 97 of 98 treatment-failure patients with sequencing data. One relapser patient (genotype 1b) did not have any known DNV resistance mutations by population sequencing. The R155K mutation was detected in all genotype 1a patients. In contrast, both R155K (5/19 cases) and D168 (14/19 cases) mutations were observed in genotype 1b patients. Of the 99 patients with NS5B sequencing data, only 1 genotype 1a patient had the MCB resistance mutation NS5B L159F/L+L320F and 2 genotype 1a had the S282T mutation (both from Arm B).

SAFETY RESULTS

Over the course of the study, there were no deaths and one pregnancy was reported. Urinalysis, vital signs, and ECG results were generally unremarkable and similar across treatment groups over the course of the study.

Main Protocol

Most patients (92-100% and 2 of 3 patients in Group B12/Placebo) experienced at least one AE; AE incidence was similar across treatment groups. Few AEs were of severe intensity and few patients withdrew from the study due to AEs. Few patients experienced AEs that led to dose modification (4 patients [2%]) or dose interruption (3 patients [2%]).

Overview of Adverse Events (Main Protocol): Safety Population

	Group A12/RBV N=17	Group A24/RBV N=66	Group B12/Placebo N=3	Group B24/Placebo N=83
	Patients, n (%)			
Any AE	17 (100)	64 (97)	2	76 (92)
Severe AE	2 (12)	2 (3)	0	2 (2)
Any SAE	1 (6)	1 (2)	0	5 (6)
AE leading to withdrawal from:				
MCB	0	1 (2)	0	1 (1)
DNV	0	1 (2)	0	1 (1)
RTV	0	1 (2)	0	1 (1)
RBV/Placebo	0	1 (2)	0	2 (2)
Deaths	0	0	0	0
Pregnancy	0	0	0	1

Seven patients experienced 7 SAEs. One patient in Group B24/Placebo experienced a suspected unexpected serious adverse reaction (SUSAR) of abdominal pain considered to be related to erythromycin and remotely related to DNV/r, MCB, and placebo. The patient was treated for the event, which resolved without sequelae.

Marked low hemoglobin abnormalities were reported more frequently among patients in Arm A than Arm B, likely due to the co-administration of RBV in Arm A. In Group A24/RBV, mean hemoglobin values were below the lower limit of normal (LLN) from Week 4 to Week 24. The incidence of marked chemistry abnormalities, and the incidence of ACTG Grade 3 or 4 abnormalities, was low and similarly observed among the treatment groups; no specific trends were noted. Grade 4 ALAT abnormalities were reported in 2 patients, one each from Group A24/RBV and Group B24/Placebo; both occurred at least 4 weeks after last dose and were associated with virologic failure.

PEG-IFN/RBV Extension (Arm B)

No safety concerns were raised during the PEG IFN/RBV Extension. Of the 44 patients, 43 (98%) experienced at least one AE and 4 patients (9%) reported 5 SAEs. All SAEs were considered unrelated to study medication, except in one patient with suicide attempt. This event was considered related to PEG-IFN and previous depression. Seven patients experienced AEs that led to withdrawal of any study treatment and 6 patients experienced AEs that led to dose reduction in PEG-IFN and/or RBV.

Marked low absolute neutrophil count was reported in 70% of patients and marked low lymphocyte count was reported in 41% of patients. Incidence of Grade 3 and 4 neutropenia was 7% and 2%, respectively, and incidence of Grade 3 and 4 lymphopenia was 18% and 5%, respectively.

CONCLUSIONS

This is the first study that evaluated SVR24 in HCV genotype 1-infected, treatment naïve patients treated with the IFN-free combination of the DAA's MCB and DNV/r for 12-24 weeks. Efficacy of the regimen, with or without RBV, was not established irrespective of treatment duration. In the RBV-containing treatment arm (Arm A), SVR24 rates were 17.6% (95% CI: 6.2, 41.0%) for Group A12/RBV and 37.9% (95% CI: 27.1, 49.9%) for Group A24/RBV. Unacceptably high early relapse rates and very low SVR24 (2 of 86 patients [2.3%]) in the RBV placebo arm (Arm B) indicate that the MCB and DNV/r combination without RBV is not an effective treatment regimen for patients infected with HCV genotype 1. HCV genotype subgroup analysis performed in Arm A patients showed higher SVR24 in genotype 1b-infected patients than in genotype 1a-infected patients (16 of 27 patients [59.2%] and 12 of 56 patients [21.4%], respectively). No clear impact of IL28B haplotype was observed. The majority of treatment failures was associated with virologic relapse. Population sequencing at the time of

relapse identified mutations associated with DNV resistance in 97 of 98 evaluable patients, suggesting that drug resistance contributes to treatment failure.

Treatment with MCB and DNV/r for up to 24 weeks in IFN-naïve HCV genotype 1 infected patients was safe, well tolerated, and did not raise any safety issues. Additionally, the safety profile of the subset of patients who received MCB and DNV/r combination therapy with RBV for 12-24 weeks or with placebo for 12-24 weeks, followed by PEG-IFN and RBV for up to 24 weeks, was generally as expected for RBV or PEG-IFN/RBV and did not reveal any new safety concerns.