ISYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL NV21075/D)

COMPANY: Hoffmann-La Roche, Inc NAME OF FINISHED PRODUCT: RO5190591, danoprevir NAME OF ACTIVE SUBSTANCE(S): RO5190591	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A Randomized, Partially-Blind Study to Evaluate the Safety, Tolerability and Effect on Virological Response of Treatment with the HCV Protease Inhibitor RO5190591 in combination with Pegasys® and Copegus® for 12 weeks, versus treatment with Pegasys® and Copegus® alone, in treatment-naïve Patients with Chronic Hepatitis C Genotype 1 Virus Infection Report No. [redacted]. IND No. 73,712 EUDRACT No. 2009-009608-38 Date of Report: Version 1: May 2012; Version 2: August 2012 (to include CSR synopsis)
INVESTIGATORS / CENTERS AND COUNTRIES	Australia (4); Canada (8); France (3); Germany (2); Italy (1); United States (23)
PUBLICATION (REFERENCE)	*Reports* [redacted]. Sequencing and phenotypic characterization of NS3/4A and NS3 protease clinical isolates from HCV infected patients enrolled in the clinical trial NV21075-interim analysis. Research Repository No. [redacted]. [redacted]. Sequencing and phenotypic characterization of NS3/4A and NS3 protease clinical isolates from HCV infected patients enrolled in the clinical trial NV21075-2nd interim analysis. Research Repository No. [redacted]. [redacted]. Sequencing and phenotypic characterization of NS3/4A and NS3 protease clinical isolates from HCV infected patients enrolled in the clinical trial NV21075-final report. Research Repository No. [redacted]. [redacted]. Sequencing characterization of NS3/4A or NS3 protease clinical isolates from HCV infected patients enrolled in the clinical trial NV21075 that experienced either a viral breakthrough while on PEG-IFN/Ribavirin, a relapse or discontinued before the end of

therapy. Research Repository No. [redacted].

MedWatch 668721; November, 2009.

MedWatch 677735; January, 2010.

MedWatch 678494; January, 2010.

MedWatch 684134; February, 2010.

Conference Presentations

Terrault N, Cooper C, Balart LA, Larrey DG, Box TD, Yoshida EM, Lawitz E, Buggisch P, Ferenci P, Weltman M, Labriola-Tompkins E, Zhang Y, Navarro MT, Lim CY, Yetzer ES, Marcellin P. Phase II randomised, partially-blind, parallel-group study of oral danoprevir (RG7227) with PEGIFNα-2A (PEGASYS®) plus ribavirin in treatment-naive genotype 1 patients with CHC: Results of planned week 12 interim analysis of the atlas study. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. Hynes Convention Center October 30-November 3, 2010.

Le Pogam S, Chhabra M, Yan JM, Ilnicka M, Ji Y, Chin DJ, Gonzaludo N, Klumpp K, Najera I. Low rate of viral load rebound observed among treatment-naive genotype 1 patients with chronic hepatitis C treated with danoprevir (RG7227) plus PEGIFNα-2A (PEGASYS®) plus ribavirin: interim analysis. 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. Hynes Convention Center October 30-November 3, 2010.

Levi M, Frey N, Hsu JC, Jorga K, Tran J, Labriola-Tompkins L, Yetzer ES. High exposure to danoprevir (RG7227) increases the probability of ALT elevations in patients treated with danoprevir plus PegIFN α-2a (40KD) (PEGASYS) plus ribavirin. 61st Annual Meeting of the American Association for the Study of Liver, Diseases Boston, MA. Hynes Convention Center October 30-November 3, 2010.

Terrault N, Cooper C, Balart LA, Larrey DG, Box TD, Yoshida EM, Lawitz E, Buggisch P, Ferenci P, Weltman M, Labriola-Tompkins E, Thomas D, Hooper G, Zhang Y, Navarro MT, Lim CY, Yetzer ES, Marcellin P. High sustained virologic response (SVR24) rates with response-guided danoprevir (DNV; RG7227) plus PegIFN α-2a (40KD) and ribavirin (P/R) in treatment-naive HCV genotype 1 (G1) patients: Results from the ATLAS study. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. Hynes Convention Center November 9-13, 2011.

Lemenuel A, Levi M, Shulman N, Frey N. Identification of a dual mechanism of action (MoA) for danoprevir (DNV), a protease inhibitor currently in phase II, using a mechanistic viral kinetic model. 62nd Annual Meeting of the American

	Association for the Study of Liver Diseases. Boston, MA. Hynes Convention Center November 9-13, 2011. Le Pogam S, Yan JM, Chhabra M, Ilnicka M, Chin DJ, Ji Y, Zhang Y, Klumpp K, Najera I. Low prevalence of danoprevir resistance identified in genotype 1b HCV patients with prior null response treated with danoprevir plus low-dose ritonavir plus peginterferon alfa-2a (40KD)/ribavirin for 12 weeks. International Liver Congress™ 2011, 46th annual meeting of the European Association for the Study of the Liver. Berlin, Germany. Internationales Congress Centrum (ICC). March 30-April 3, 2011. Marcellin P, Cooper C, Balart LA, Larrey DG, Box TD, Yoshida EM, Lawitz E, Buggisch P, Ferenci P, Weltman M, Labriola-Tompkins E, Le Pogam S, Najera I, Thomas D, Hooper G, Shulman N, Zhang Y, Navarro MT, Lim CY, Brunda M, Yetzer ES, Terrault N on behalf of the ATLAS investigators. Response-guided danoprevir (DNV; RG7227) plus Peg-IFNα-2a and ribavirin (RBV) in ATLAS: High sustained virological response (SVR24) rates in treatment - naive hepatitis C virus (HCV) genotype 1 (G1) patients. The 22nd Conference of the Asian Pacific Association for the Study of the Liver (APASL 2012). Taipei, Taiwan. Taipei International Convention Center (TICC) February 16-19, 2012.		
PERIOD OF TRIAL	July 13, 2009 to July 4, 2011	CLINICAL PHASE	IIb
OBJECTIVES	**Primary:** Evaluated the safety, tolerability, and effect on virological response of a 12-week duration of RO5190591 in combination with pegylated interferon alfa-2a (Pegasys ® [PEG-IFN]) and ribavirin (Copegus® [RBV]) compared to the combination of PEG-IFN/RBV (standard of care [SOC]) alone in treatment-naïve Hepatitis C (HCV) patients with CHC GT1 virus infection. **Secondary:** • Evaluated the PK of RO5190591 in combination with PEG-IFN/RBV • Evaluated the viral resistance profile of RO5190591 in combination with PEG-IFN/RBV		
STUDY DESIGN	Partially-blinded, multicenter, multinational, triple therapy, Phase II trial evaluating the safety, tolerability and effect on virological response of treatment with HCV protease inhibitor RO5190591 in combination with PEG-IFN/RBV in treatment-naïve patients with chronic Hepatitis C Genotype 1 Virus infection.		
NUMBER OF SUBJECTS	• Overall: 300 (planned), 237 (actual) • Group A - 300mg RO5190591 + PEG-IFN/RBV: o 60 (planned), 73 (actual) • Group B 600mg RO5190591 + PEG-IFN/RBV: o 60 (planned), 75 (actual)		

	• Group C 900mg RO5190591 + PEG-IFN/RBV: o 60 (planned), 55 (actual) – premature discontinuation • Group D: Placebo + PEG/IFN o 30 (planned), 34 (actual) • Group E: RO5190591 (300/600/900 mg) + PEG-IFN/RBV o 60 (planned), 0 (actual) – arm canceled • Group F: Matching placebo + PEG-IFN/RBV o 30 (planned), 0 (actual) – arm canceled
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with CHC GT1 and HCV RNA ≥ 50,000 IU/mL. Patients must have been HCV treatment-naïve with a liver biopsy within 24 calendar months of the first dose showing clear absence of advanced fibrosis or cirrhosis.
TRIAL DRUG / STROKE (BATCH) No.	[redacted]
DOSE / ROUTE / REGIMEN / DURATION	RO5190591 100 mg / PO / 12 weeks RO5190591 200 mg / PO / 12 weeks
REFERENCE DRUG / STROKE (BATCH) No.	[redacted]
DOSE / ROUTE / REGIMEN / DURATION	Matching RO5190591 100 mg placebo / PO / 12 weeks Matching RO5190591 200 mg placebo / PO / 12 weeks
REFERENCE DRUG / STROKE (BATCH) No.	[redacted]
DOSE / ROUTE / REGIMEN / DURATION	RBV 200 mg F/C tablets / PO / 48 weeks
REFERENCE DRUG / STROKE (BATCH) No.	[redacted]
DOSE / ROUTE / REGIMEN / DURATION	PEG-IFN 180 μg /ml vials / SQ / 48 weeks
CRITERIA FOR EVALUATION	The “efficacy population” was defined in the protocol, in which re-randomized patients were not included. In the final analysis for CSR, “safety population” was used for all the efficacy analyses, in which the re-randomized patients were included in this population. No analyses were done based on the “per protocol” population.
EFFICACY:	The efficacy population included all patients randomized (excluding re-randomized patients) who received at least one dose of study medication and who had at least one efficacy measurement performed. The efficacy analysis population (212 patients), was performed using the safety analysis population who received at least one dose of study medication and had at least one efficacy assessment performed.

	The primary measure of efficacy was sustained virological response (SVR) defined as the percentage of patients with undetectable HCV RNA 24 weeks after end of treatment (SVR-24) Secondary assessments of efficacy were: • Virological response at clinical visits over time (undetectable [<15 IU/mL]) • Virological response at clinical visits over time <50 IU/mL • Virological response at the end of treatment period (undetectable [<15 IU/mL]) • Virological response at 12 weeks post treatment (SVR-12) • Relapse rate of patients who achieved a virological response at the end of treatment but had detectable HCV RNA at the last assessment post treatment
SAFETY:	The safety population included all patients who received at least one dose of study treatment and had had at least one post-baseline safety assessment, whether prematurely withdrawn from the study or not. Patients were assigned to treatment groups as treated (including re-randomized patients). The safety analysis population (225 patients) included all patients who received at least one dose of study medications and had at least one post-baseline safety assessment. Safety assessments evaluated in this study were adverse events (AEs), laboratory tests, vital signs, electrocardiograms (ECGs), dose adjustments and premature withdrawals for safety reasons or intolerance, pregnancy testing, symptom directed physical exams and ophthalmological exams.
PHARMACOKINETICS:	The pharmacokinetic (PK) analyses were based on the PK analysis population The RO519051 PK parameters that were analyzed for patients participating in the intensive PK assessment at Weeks 4 and 12 included: C_{max}, $AUC_{0-\tau}$, C_{min}, and and T_{max}. Patients were excluded from the PK analysis at the discretion of the clinical pharmacology scientist. Reasons for exclusion included significant violation of inclusion or exclusion criteria, significant protocol deviations or if data were unavailable. All PK parameters are presented by individual listings and summary statistics including arithmetic means, geometric means (Cmax, AUC0-τ, Cmin), median, ranges, SD, and CV. Patient listings for the Sparse DNV PK evaluations are provided separately; no further analyses were performed for this report. A population PK model was developed to describe the concentration-time profiles in all patients with evaluable PK data from NV21075.

STATISTICAL METHODS	Randomization was stratified by geographical region. Final efficacy and safety analyses on the total study population were conducted at the end of the study after all patients completed 24 weeks of treatment-free follow-up and the database was cleaned and closed. In the protocol, the 95% confidence limits of virological response rates were proposed based on the normal approximation. In the summary tables and plots of virological response, the 95% confidence intervals for the individual virological rates were calculated by the Wilson score method without continuity correction as recommended by Newcombe (references provided within the full CSR)

METHODOLOGY:

All patients received 12 weeks of triple therapy (partially blind experimental treatment RO5190591 plus PEG-IFN/RBV), followed by 12 weeks of dual therapy (PEG-IFN/RBV). Total treatment duration in this protocol was 24 or 48 weeks. Those patients in treatment groups A, B and C who achieve rapid virological response (RVR - defined as undetectable HCV RNA by Week 4), and who remained undetectable through to Week 20 (referred to as extended RVR) were to stop treatment at Week 24. All other patients in treatment groups A, B and C were to receive PEG-IFN/RBV for an additional 24 weeks for a total treatment of 48 weeks. All patients in Group D were to receive 48 weeks of PEG-IFN/RBV.

All treatment groups were to have a 24-week RO5190591 treatment-free follow-up period.

Viral load collected during each weeks were first logarithmically (based 10) transformed. Results falling below the Roche COBAS TaqMan HCV test limit for quantification were set to the lower limit of the assay's linear range prior to the analyses. This data were presented by listings, and summary statistics including means, medians, standard error, confidence interval for means, ranges, and coefficient of variation at individual visits.

Virological response rates and their corresponding 95% confidence limits based on binomial probabilities were summarized at each visit for each treatment group. No formal statistical pairwise treatment comparisons were made.

The safety and tolerability data were presented in individual listings and summary tables and graphs where applicable.

All pharmacokinetic parameters were listed and summarized. The log10-transformed viral load and viral response status at individual visits were presented in individual listings, summary tables and graphs where applicable.

EFFICACY RESULTS:

In the analysis of the primary efficacy endpoint, SVR-24 according to the actual treatment period, the three experimental treatment groups showed numerically higher SVR24 rates over the SOC group. The individual SVR-24 rates for 300 mg, 600 mg, 900 mg and the SOC groups were 68%, 85%, 76%, and 42%, respectively, and the 600 mg group achieved the highest SVR24 rate among the three experimental treatment groups.

There was a dose-dependent response at Week 2 with 53%, 54%, and 60% of patients achieving RVR in the 300 mg, 600 mg and 900 mg groups, respectively, compared to 0 patients in the SOC group who achieved RVR at Week 2. At Week 4, higher rates of RVR were achieved in the three RO5190591 treatment groups (74%, 88% and 86%), compared to the SOC group (7%). The cEVR rates were also numerically higher in the 300 mg, 600 mg and 900 mg groups (88%, 92%, and 94%) than the SOC group (42%). The conclusions for the mean change from baseline HCV RNA profiles were consistent with those for the virological response profiles.

The end-of-treatment response rates were numerically higher in the three RO5190591 treatment groups (86%-94%) than the SOC group (68%). The RO5190591 treatment groups showed numerically lower relapse rates than the SOC group. The individual relapse rates for 300 mg,

600 mg, 900 mg and the SOC groups were 18%, 8%, 11%, and 38%, respectively, and the 600 mg group achieved the lowest relapse rate among the three treatment groups. The 12 weeks post treatment relapse rates were very similar to the 24-weeks post-treatment relapse rates.

For the subgroup of patients for which an IL28B genotype was available, in the genotype CC patients SVR-24 according to the actual treatment period in the 300 mg and 900 mg groups (81% and 85%) was lower than observed in the SOC group (88%), but SVR-24 in the 600 mg group (95%) was numerically higher than that of the SOC group. In genotype non-CC patients, SVR-24 according to the actual treatment period was numerically much higher in the three treatment groups (63%-79%) than in the SOC group (25%).

SAFETY RESULTS:

RO5190591 was well tolerated in subjects at doses up to 600 mg. The 900 mg group was discontinued during the study due to safety concerns of three cases of Grade 4 ALT elevations. The majority of AEs were mild or moderate in intensity and there were no differences in the number of severe AEs across the four groups.

There were a total of 17 SAEs in the pooled RO5190591 group (14/194 patients [7%]) and 6 in the SOC group (6/31 patients [19%]) including one death in the 600 mg group that was considered to be unrelated to study treatment. Four patients experienced a total of 5 SAEs that were considered by the investigator to be related to RO5190591 (ALT increased, ascites, pulmonary embolism/deep venous thrombosis, and supraventricular tachycardia). The most common SAE across all groups was infection.

PHARMACOKINETIC RESULTS:

Serial PK samples from predose and up to 8 hours (for q8h regimen) or 12 hours (for q12h regimen) post-dose were collected for measurement of RO5190591 in approximately 20% of patients at Weeks 4 and 12. Peak plasma concentrations were reached after a median of 0.5 – 1.0 hours across all dose groups. RO5190591 exposures as measured by C_{max} and $AUC_{0-\tau}$ exhibited high variability on both Week 4 and Week 12.

In order to compare exposures across regimens with different dosing frequencies, $AUC_{0-\tau}$ was normalized to AUC_{0-24h}. Week 4 RO5190591 exposures as measured by geometric mean AUC_{0-24h} increased dose proportionally between the 300 mg and 600 mg groups. However, RO5190591 exposure increased more than dose proportionally, between 300 mg and 900 mg and between 600 mg and 900 mg. A 2-fold increase in total dose (300 mg vs 900 mg) resulted in a 4-fold increase in $AUC_{0-24h.}$ Similarly, a 1.5 increase in dose between 600 mg and 900 mg resulted in a 2.5-fold increase in $AUC_{0-24h.}$ A population PK model was developed and reported separately.

CONCLUSIONS:

Analysis of the safety data from 144 patients treated with RO5190591 showed that treatment with 300 mg and 600 mg was safe and well tolerated. The 900 mg group was discontinued due to three cases of Grade 4 ALT elevations.

A total of 19 patients, all infected by a GT1a virus, developed RO5190591 resistance (8 while on RO5190591 treatment and 11 after the end of RO5190591 therapy).

Rapid and profound reduction in serum HCV RNA levels was demonstrated. SVR24 rates and end-of-treatment response rates were higher in the RO5190591 treatment groups along with lower relapse rates than the placebo + SOC group. SVR24 rates were highest in the 600 mg and, importantly, the majority of patients in this group achieved an RVR and were eligible for a shortened treatment regimen.