SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL NV19865F)

COMPANY: F. Hoffmann La Roche Ltd. NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): RO4588161, PEG-IFN alfa-2a, ribavirin	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A phase II, randomized, double-blinded, multicenter, dose finding study evaluating the efficacy and safety of the HCV polymerase inhibitor prodrug (RO4588161) when given in combination with Pegasys® and Copegus® versus the currently approved combination of Pegasys® and Copegus® in treatment-naive patients with chronic hepatitis C genotype 1 virus infection/ Report No. [redacted] February 2010.		
INVESTIGATORS / CENTERS AND COUNTRIES	A total of 64 centers in Australia, Austria, Canada, France, Germany, Italy, Spain, and the United States		
PUBLICATION (REFERENCE)			
PERIOD OF TRIAL	November 11, 2007, to August 4, 2009	CLINICAL PHASE	IIB
OBJECTIVES	**Primary:** To determine the optimal treatment combination based on the efficacy and safety of the HCV polymerase inhibitor prodrug (RO4588161) in combination with PEG-IFN alfa-2a (abbreviated hereafter as PEG-IFN) and ribavirin (RBV) versus the currently approved combination of PEG-IFN and RBV in treatment-naive patients with chronic hepatitis C genotype 1 virus infection. **Secondary:** • To evaluate the pharmacokinetics of RO1048297 (the parent compound of RO4588161) when administering RO4588161 in combination with PEG-IFN and RBV (Results are not presented in this report.) • To evaluate the resistance profile of RO4588161 in combination with PEG-IFN and RBV		
STUDY DESIGN	In this double-blind, active-controlled, parallel-group study, patients were randomized to one of 7 treatment groups: Group A: RO4588161 1000 mg twice daily (bid) + PEG-IFN 180 μg + RBV 1000/1200 mg for 24 weeks followed by PEG-IFN 180 μg + RBV 1000/1200 mg (standard of care [SOC]) for 24 weeks ("1000/180") Group B: RO4588161 500 bid + PEG-IFN 180 μg + RBV 1000/1200 mg for 24 weeks followed by SOC for 24 weeks ("500/180") Group C: RO4588161 500 mg bid + PEG-IFN 180 μg + RBV 1000/1200 mg for 24 weeks in patients who achieve a rapid virological response (RVR) and maintain undetectable HCV RNA through week 22, and for 48 weeks in patients without RVR ("500/180 RVR") Group D: RO4588161 1500 mg bid + PEG-IFN 90 μg + RBV 1000/1200 mg for 24 weeks followed by SOC for 24 weeks		

	(“1500/90”) Group E: RO4588161 1000 mg bid + PEG-IFN 90 µg + RBV 1000/1200 mg for 24 weeks followed by SOC for 24 weeks (“1000/90”) Group F: RO4588161 500 mg bid + PEG-IFN 90 µg sc qw + RBV 1000/1200 mg for 24 weeks followed by SOC for 24 weeks (“500/90”) Group G: SOC for 48 weeks By protocol amendment, the duration of treatment with RO4588161 and the duration of the double-blind treatment period was shortened to 12 weeks. Thereafter, all treatment was open label. See Methodology for other changes in study design. Patients from all treatment groups were to participate in a 24-week follow-up period after treatment.
NUMBER OF SUBJECTS	Approximately 490 patients were to be equally randomized to the 7 treatment groups. A total of 512 patients were randomized, and 504 (70 to 75 per treatment group) had at least 1 dose of study medication.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Males and females 18 to 65 years old with treatment-naive, chronic HCV genotype 1 infection and HCV RNA ≥ 50 000 IU/mL. Patients with other forms of liver disease, anemia, HIV infection, hepatocellular carcinoma, pre-existing severe depression or other psychiatric disease, cardiac disease, renal disease, uncontrolled seizure disorders, or severe retinopathy were excluded. No more than 20% of the patients enrolled were to have liver cirrhosis or transition to/incomplete cirrhosis.
TRIAL DRUG / STROKE (BATCH) No.	HCV polymerase inhibitor prodrug RO4588161 500-mg tablets in bottles of 500-mg doses/ batch No. [redacted]; in boxes of 500-mg doses/ batch Nos. [redacted], and [redacted]; in boxes of 1000-mg doses/ batch Nos. [redacted], and [redacted]; and in boxes of 1500-mg doses/ batch Nos. [redacted], and [redacted]. PEG-IFN 180 µg in 1 mL packaged in 2-mL vials/ batch Nos. [redacted], and [redacted]. PEG-IFN 90 µg in 1 mL packaged in 2-mL vials/ batch Nos. [redacted], and [redacted] RBV 200-mg tablets in bottles/ batch Nos. [redacted], [redacted] and [redacted].
DOSE / ROUTE / REGIMEN / DURATION	See Study Design for a list of regimens and their durations. PEG-IFN was administered subcutaneously (sc) once weekly (qw). RO4588161 and RBV were administered by mouth (po) bid with meals. The RBV total daily dose was 1000 mg for patients weighing <75 kg and 1200 mg for patients weighing ≥ 75 kg.
REFERENCE DRUG / STROKE (BATCH) No.	RO4588161 placebo (batch Nos. [redacted] and [redacted] administered with SOC therapy
DOSE / ROUTE / REGIMEN / DURATION	SOC for 48 weeks; included RO4588161 placebo for first 24 weeks (changed to 12 weeks by protocol amendment).
CRITERIA FOR EVALUATION	
EFFICACY:	The primary measure of efficacy was sustained virological response (SVR), defined as the percentage of patients with undetectable HCV RNA as measured by the Roche COBAS TaqMan HCV Test

	(detection limit = 15 IU/mL) 24 weeks after the end of treatment. Patients without HCV RNA measurements at the end of the 24-week follow-up period were considered non-responders. Other measures of efficacy were HCV RNA concentrations and percentages of patients with undetectable HCV RNA at each visit.
PHARMACODYNAMICS	Serum samples were collected for phenotypic and genotypic analyses of RO1048297 resistance in patients who experienced either viral load rebound or non-response while on treatment with RO4588161.
SAFETY:	Clinical adverse events, treatment discontinuations and dose modifications due to adverse events or laboratory abnormalities, laboratory test results, vital signs
STATISTICAL METHODS	Mean, standard deviation, standard error, median, minimum, and maximum were determined for continuous variables. Number and percentage were determined for categorical variables.

METHODOLOGY:

HCV RNA was measured at each visit, including visits at 4, 12, and 24 weeks after the end of treatment. Discontinuation of treatment was required for patients who did not demonstrate evidence of a virological response (defined as ≥ 2 $\log_{10}$ drop in HCV RNA titer by week 12. Patients were evaluated for safety throughout treatment and follow-up.

By protocol amendment, RO4588161 treatment in the 1500/90 group was stopped, and patients in that group were switched to SOC. Also, all patients discontinued treatment with RO4588161 or its placebo and blinded PEG-IFN at week 12, or immediately for patients already past week 12. Patients were switched to SOC. Patients in the 500/180 RVR group who achieved the RVR criteria (undetectable HCV RNA at week 4, remaining undetectable through week 22) stopped treatment at week 24. Patients in the 500/180 RVR group who did not achieve an RVR remained on SOC to receive a total of 48 weeks of treatment. Subsequent protocol amendments required discontinuation of study medication in patients with grade 4 lymphopenia (<200 cells/mm^3), close monitoring in those patients and in patients with lymphocyte counts < 500 cells/mm^3, and discontinuation of study treatment in patients who had received RO4588161.

EFFICACY RESULTS:

During 12 weeks of treatment with RO4588161 in combination with PEG-IFN and RBV, HCV RNA concentration decreased in a dose-dependent manner. RVR (undetectable HCV RNA at week 4) was numerically highest in the 1000/180 and 1500/90 groups and lowest in the 500/90 and SOC groups. Complete early virological response (undetectable HCV RNA at week 12) was numerically highest in the 1000/180 group and lowest in the SOC group. However, none of the RO4588161 groups exceeded the SOC group in virological response at 24 weeks or in SVR, which ranged from 31% to 41% (scheduled treatment period) and from 32% to 50% (actual treatment period).

PHARMACODYNAMIC RESULTS:

Twenty patients showed a viral load rebound before the end of the treatment period: 18 from the RO4588161 groups and 2 from the SOC group. Phenotypic characterization of the NS5B clinical isolates showed that susceptibility to RO1048297 and to Roferon was similar before and after the rebound occurred. Sequence analysis revealed no known RO1048297-resistance mutations or any other common amino acid substitutions selected upon treatment. The lack of phenotypic and genotypic changes indicates that the observed viral load rebound was not due to the selection of viral resistance. Furthermore, genotypic characterization of the NS5B clinical isolates from all baseline samples showed no resistance mutation S96T or S96T/N142T.

SAFETY RESULTS:

The 6 regimens of RO4588161 in combination with PEG-IFN and RBV were not tolerated. New, unexpected safety problems were identified.

The cumulative doses of RO4588161 were at or near the expected values for the first 4 weeks of treatment but decreased thereafter because of safety-related dose modifications and discontinuations of treatment. Later in the course of treatment, the percentages of the expected cumulative doses of PEG-IFN and RBV were less in the RO4588161 groups (except for the 500/90 group) than in the SOC group.

Lymphopenia reported as an adverse event was frequent in the RO4588161 groups, occurring in 29% to 45% of patients, compared with 3% of patients in the SOC group. Other frequent adverse events, including

fatigue, headache, insomnia, nausea, myalgia, and chills, were relatively evenly distributed across treatment groups. Infections occurred in 45% to 51% of patients per group. Eye disorders were more frequent in the RO4588161 groups (except for the 500/180 RVR group) than in the SOC group.

Three deaths occurred in RO4588161 groups. The causes of death were cardiac arrest (in a patient who had lymphoma that progressed quickly) and suicide (both in the 500/180 RVR group), and fulminant disseminated varicella (1500/90 group). One patient in the SOC group died in a road traffic accident.

Serious adverse events were more frequent in the 1000/180 and 1500/90 groups (20%, 17%) than in the other groups (4% to 11%). Also, serious infections were more frequent in the 1000/180 and 1500/90 groups (5% and 6%, respectively) than in other groups (0% to 3%). Serious ocular events occurred in 5 patients in the 1500/90 group and 3 patients in the 1000/90 group. All of the 8 serious ocular events led to discontinuation of study medication. Six of the events resolved. One patient was lost to follow-up. One patient is still being followed but has reported improvement.

Adverse events and laboratory abnormalities led to withdrawal of 28% to 36% of patients from RO4588161. Withdrawal from PEG-IFN was much more frequent in the RO4588161 groups (23% to 45%) than in the SOC group (8%); results were similar for withdrawal from RBV. Lymphopenia accounted for most of the withdrawals from RO4588161, PEG-IFN, and RBV in the RO4588161 groups.

The percentages of patients with dose modifications of RO4588161, PEG-IFN, and RBV were related to the dose of RO4588161. Most of the dose modifications were due to laboratory abnormalities. Neutropenia was the most frequent laboratory abnormality leading to dose modification of RO4588161 and PEG-IFN, whereas anemia was the most frequent laboratory abnormality leading to dose modification of RBV.

Mean decreases from baseline over time in WBC counts, lymphocytes, neutrophils, platelets, and RBC parameters were greater in the RO4588161 groups (except for the 500/90 group) than in the SOC group. Mean values for lymphocyte counts decreased progressively during 12 weeks of treatment with RO4588161 and remained low during subsequent treatment with SOC. The mean decreases in platelets and RBC parameters were related to RO4588161 dose. Grade 4 leukopenia (WBC count $< 1.0 \times 10^9$/L), grade 3 lymphopenia (lymphocyte count $<0.5 \times 10^9$/L), grade 4 neutropenia (neutrophil count $<0.5 \times 10^9$/L), RBC count $< 3.2 \times 10^{12}$/L, and hematocrit < 0.3 were more frequent in the RO4588161 groups than in the SOC group. Grade 4 thrombocytopenia (platelet count $<20 \times 10^9$/L) and hemoglobin concentration <8.5 g/dL were more frequent in the higher dose RO4588161 groups (1000/180 and 1500/90) than in the SOC group.

ASAT and ALAT decreased in all groups. Haptoglobin showed a prolonged increase in RO4588161 groups, except for the 500/90 group. Ferritin increased in all groups, with larger mean increases in the groups that received PEG-IFN 180 µg than in the groups that received PEG-IFN 90 µg. Increases in amylase and lipase occurred at week 12 in the 1000/180, 1500/90, and 1000/90 groups.

CONCLUSIONS:

The following 6 combination regimens containing RO4588161, PEG-IFN, and RBV showed efficacy early in the course of treatment but were not tolerated by HCV genotype 1 patients: 1000 mg RO4588161 bid/180 µg PEG-IFN qw, 500 mg RO4588161 bid/180 µg PEG-IFN, 500 mg RO4588161 bid/180 µg PEG-IFN with duration guided by RVR, 1500 mg RO4588161 bid/90 µg PEG-IFN, 1000 mg RO4588161 bid/90 µg PEG-IFN, and 500 mg RO4588161 bid/90 µg PEG-IFN, each in combination with RBV 1000 or 1200 mg. Progressive, severe lymphopenia developed during 12 weeks of treatment with RO4588161. Severe neutropenia, severe anemia, serious ocular events, and serious infections also occurred in RO4588161 groups.