SYNOPSIS OF ABBREVIATED RESEARCH REPORT [redacted] (PROTOCOL NB19751)

COMPANY: Hoffmann-La Roche Ltd. NAME OF FINISHED PRODUCT: palovarotene NAME OF ACTIVE SUBSTANCE(S): RO3300074	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A double-blind, placebo-controlled efficacy (as assessed by post-bronchodilator FEV_1) and safety study of 5 mg RO3300074 once-daily for 2 years in subjects with smoking-related, moderate-to-severe COPD with emphysema receiving concurrent optimal COPD drug therapy / Date of Report: November 2011		
INVESTIGATORS / CENTERS AND COUNTRIES	Conducted in 61 centers in the USA, Europe (Bulgaria, Czech Republic, Hungary, Iceland, Italy, Latvia, Poland, Ukraine, and UK), Israel, and South Africa.		
PUBLICATION (REFERENCE)	None.		
PERIOD OF TRIAL	January 09, 2007 to May 24, 2010	CLINICAL PHASE	2
OBJECTIVES	The primary objective was to investigate and compare the efficacy, safety, and tolerability of 5-mg RO3300074 with placebo given once daily in COPD patients with emphysema, while all patients were also treated with optimal COPD drug therapy.		
STUDY DESIGN	Randomized, multi-center, double-blind, placebo-controlled.		
NUMBER OF SUBJECTS	492 randomized, 489 dosed (330 with RO3300074 and 159 with placebo), 339 completed.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	The target population consisted of patients > 44 years of age with symptomatic smoking-related moderate to severe COPD with emphysema, as defined by a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/ forced vital capacity (FVC) ratio < 70%, a post-bronchodilator FEV_1 value at randomization visit ≥ 35% and ≤ 70% of the predicted normal value, and a lung carbon monoxide diffusing capacity (Dl,co [Tl,co]) value < 70% of the predicted normal value for gender, age, and height.		
TRIAL DRUG / STROKE (BATCH) No.	2.5-mg RO3300074 soft gelatin capsule packaged in 2-oz HDPE bottles / Batch number: [redacted].		
DOSE / ROUTE / REGIMEN / DURATION	5 mg of RO3300074 (two 2.5-mg soft-gelatine capsules) orally once daily for 24 months.		

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REFERENCE DRUG / STROKE (BATCH) No.	Matching placebo / Batch number: [redacted].
DOSE / ROUTE / REGIMEN / DURATION	Two matching placebo soft-gelatine capsules orally once daily for 24 months.
CRITERIA FOR EVALUATION	
SAFETY:	Adverse events, laboratory abnormalities, vital signs.
STATISTICAL METHODS	The safety parameters were analyzed descriptively.

METHODOLOGY:

Patients were randomly assigned to receive either 5 mg of RO3300074 or placebo for 24 months. Safety parameters were followed in each study visit and during the study follow-up visit performed 28 days after the last study drug dose administration.

EFFICACY RESULTS:

The primary efficacy parameter was post-bronchodilator FEV_1. [redacted] this study report is prepared as an abbreviated study report. The abbreviated study report NB19751 provides a full safety presentation with the safety data being summarized descriptively. The major efficacy data are attached as data displays to this report without text descriptions in the body of the report. The pharmacokinetic data are not analyzed and reported.

SAFETY RESULTS:

The incidence of adverse events (91.5% for RO3300074 and 81.8% for placebo) and treatment-related adverse events (70.5% for RO3300074 and 42.8% for placebo) was higher in patients treated with RO3300074 than in patients treated with placebo. The difference in the incidence of adverse events between the two treatment groups was largely accounted for by a higher incidence of skin and subcutaneous tissue disorders (65.3% vs 31.4%), gastrointestinal disorders (41.3% vs 25.2%), and musculoskeletal and connective tissue disorders (20.7% vs 12.6%) in the RO3300074-treated patients, which in turn mainly reflected an increased incidence of mucocutaneous events in the RO3300074 group (69.0%) compared with that in the placebo group (37.7%). The higher incidence of musculoskeletal and connective tissue disorders in the RO3300074 group was largely due to a more frequent reporting of arthralgia, muscle spasms, and musculoskeletal pain in RO3300074-treated patients.

Most of the frequently seen adverse events (incidence ≥ 5%) were either mucocutaneous adverse events such as dermatitis, cheilitis, dry skin, conjunctivitis, etc, which showed a higher incidence in the RO3300074 group than in the placebo group, or events likely reflecting the exacerbation of the patients' underlying respiratory illness such as chronic obstructive pulmonary disease, upper respiratory tract

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infection, pneumonia, bronchitis, etc, which usually had a similar incidence in the two treatment groups or a slightly higher incidence in the placebo group than in the RO3300074 group. The most frequently seen treatment-related adverse events (incidence ≥ 5%) included dermatitis, dry skin, pruritus, alopecia, skin exfoliation, rash, cheilitis, dry mouth, lip dry, conjunctivitis, rhinitis, etc, all showing a higher incidence in the RO3300074 group and being mucocutaneous events. The majority of adverse events and mucocutaneous events in both treatment groups were mild or moderate in intensity. In addition, the majority of mucocutaneous adverse events in both treatment groups were CTC grade 1 or 2 events. Grade 3 mucocutaneous events were reported in 38 patients (11.5%) treated with RO3300074 and 3 patients (1.9%) treated with placebo, and grade 4 mucocutaneous events were reported in 2 patients (0.6%) treated with RO3300074. Study drug dose modifications were made in the majority of cases for grade 3 or 4 mucocutaneous events. Treatment withdrawals for mucocutaneous events occurred in 18 patients (5.5%) treated with RO3300074 and 1 patient (0.6%) treated with placebo.

The incidence (12.5% with RO3300074 and 13.2% with placebo) and rate of neoplasms (14.9 and 16.3 events per 100 patients treated with RO3300074 and placebo, respectively) were comparable for the two treatment groups. Further analysis indicated that the rate of benign (1.8 and 2.5 events per 100 patients treated with RO3300074 and placebo, respectively) or malignant neoplasms (6.7 and 6.3 events per 100 patients treated with RO3300074 and placebo, respectively) and specifically the rate of lung malignant neoplasms (2.1 and 2.5 events per 100 patients treated with RO3300074 and placebo, respectively) were all comparable between the two treatment groups.

With the chest CT scan, 41.9% and 44.6% of patients in the RO3300074 and placebo groups, respectively, were detected to have at least 1 lung nodule at baseline and, of the patients with lung nodule(s) detected at baseline, the majority (92.7% for RO3300074 and 94.3% for placebo) had lung nodule(s) ≤ 8 mm. During study treatment up to week 104, the percentage of patients with at least 1 lung nodules increased to 50.2% in the RO3300074 group compared with 44.9% in the placebo group. For RO3300074-treated patients, the percentage of patients with lung nodules > 8 mm increased from 7.2% at baseline to 16.4% at week 52 but decreased to 10.8% at week 104. The data for placebo-treated patients followed a similar pattern of changes. On the basis of these data, no convincing evidence was present to suggest a clear effect of RO3300074 on the CT scan-detected lung nodules.

Compared with placebo treatment, RO3300074 treatment did not show an increased rate of serious adverse events (29.8% for RO3300074 and 26.4% for placebo) or treatment-related serious adverse events (2.4% for RO3300074 and 3.1% for placebo). The most frequent serious adverse events were those belonging to the body system of infections or infestations, neoplasms (including benign, malignant, and unspecified), and respiratory, thoracic, and mediastinal disorders, and cardiac disorders. The incidence of the serious adverse events under each of these disease body systems was also similar between the two treatment groups. The most frequent single serious adverse event was pneumonia, which accounted for a large part of serious infections in both treatment groups (5.5% and 5.0% for RO3300074 and placebo, respectively), and was presumably related to the patients' underlying COPD.

The rate of deaths was the same for the two treatment groups. This was the case for the deaths that occurred within 42 days post-treatment (2%) as well as for the deaths that were reported beyond 42 days

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following the last dose (3%). All deaths were considered unrelated to study treatment by the investigator.

The rate of treatment withdrawals for adverse events (20.7% for RO3300074 and 15.1% for placebo) and study drug dose modifications (26.1% for RO3300074 and 17.0% for placebo) was higher in patients in the RO3300074 group than in those in the placebo group. The different rates were again largely accountable by mucocutaneous events associated with RO3300074 treatment. For treatment withdrawals, compared with 1 placebo-treated patients (0.6%), 17 RO3300074-treated patients (5.2%) withdrew from study treatment for events reported as skin and subcutaneous tissue disorders, such as dermatitis, erythema, rash, dry skin, etc, all of which belonged to mucocutaneous events. Study drug dose modifications included dose interruption and dose reduction. In the two treatment groups, the rate of dose interruptions was similar (13.1% for RO3300074 and 13.8% for placebo). A higher rate of dose modifications was observed in the RO3300074 group (26.1%) than in the placebo group (17.0%), which was due to a higher rate of dose reductions in the RO3300074 group. In fact, the rate of both the temporary and permanent dose reductions was higher in RO3300074-treated patients. The differences were mostly due to a higher percentage of RO3300074-treated patients having dose reductions for mucocutaneous adverse events.

Marked liver enzyme elevations were observed in a higher proportion of patients treated with RO3300074 than of those treated with placebo (high GGT: 10.1% for RO3300074 vs 3.8% for placebo; high ALT: 2.8% for RO3300074 vs 1.3% for placebo; high AST: 2.5% for RO3300074 vs 1.3% for placebo). However, most of these abnormalities were isolated increases which disappeared after repeated measurements in most of the cases. In addition, these abnormalities were not accompanied by other liver function test abnormalities and also not associated with clinical signs of liver toxicity. Additionally, 13.4% of patients receiving RO3300074 shifted their serum triglyceride level from grade 0 at baseline to grade 1 during study treatment, which were more frequent than 7.5% of patients receiving placebo who had the same degree of shift. Two additional RO3300074-treated patients had a shift of triglyceride value from grade 1 at baseline to grade 2 during study treatment. Shifts of liver enzyme, amylase, and lipase values were also seen. Most of these shifts were from grade 0 at baseline to grade 1 during study treatment, and no clear trends of a more frequent shift of the liver enzyme values or amylase/lipase values to a higher grade were seen with RO3300074 treatment as compared with placebo treatment.

No differences of clinical importance in vital sign abnormalities between the two treatment groups were observed.

CONCLUSIONS:

RO3300074 given orally at 5.0 mg once daily for the treatment duration of up to 24 months was well tolerated by moderate to severe COPD patients with emphysema. Compared with placebo, the major finding of the safety profile of RO3300074, as has been known before, was increased occurrence of mucocutaneous events, which was manageable with clinical procedures.