SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NP22383)

COMPANY: F. Hoffmann-La Roche Ltd. NAME OF FINISHED PRODUCT: Not available NAME OF ACTIVE SUBSTANCE(S): RO4929097	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A phase II study of orally administered RO4929097, a gamma-secretase inhibitor, as a single agent in patients with recurrent or refractory Non-Small Cell Lung Cancer (NSCLC) / Report No. [redacted] 07 March 2011.		
INVESTIGATORS / CENTERS AND COUNTRIES	[redacted] The Netherlands.		
PUBLICATION (REFERENCE)	None at the time of publication.		
PERIOD OF TRIAL	15 January 2010 to 03 August 2010	CLINICAL PHASE	II

OBJECTIVES

Primary

- To evaluate the effect of RO4929097 on tumor blood flow and tumor metabolic activity.

Secondary

- To evaluate the effect of RO4929097 on the following pharmacodynamic (PD) parameters:
  - Changes in circulating endothelial precursors (cEPCs)
  - Changes in circulating hematopoietic progenitor cells (cHPCs)
  - Changes in the soluble markers of angiogenesis
  - Changes in Aβ-40 levels
  - Changes in urine endothelial cells
  - Changes in skin biopsy tissue
- To evaluate the pharmacokinetic (PK) profile of RO4929097, assessed in the first 2 cycles of therapy. PK data were modeled with PD and response assessment data.
- To characterize overall safety and tolerability of RO4929097 in this patient population.
- To evaluate RO4929097 anti-tumor activity in this indication, assessed by:
  - Response rate (Response Evaluation in Solid Tumors [RECIST])
  - Time to tumor progression (TTP)
- To perform an exploratory analysis of both baseline response-predictive markers and PD markers.

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STUDY DESIGN	An open-label, exploratory, single-center, phase II study of RO4929097.
NUMBER OF SUBJECTS	**Planned:** Up to 32 evaluable patients, 12 patients in Cohort 1 and 20 patients in Cohort 2.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult male or female patients, 18 years of age or older, with Stage IIIB/IV histologically-confirmed NSCLC that was recurrent or refractory to no more than 2 lines of therapy for metastatic disease and who failed previous systemic treatment, or for whom no standard treatment was available and had an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
TRIAL DRUG / STROKE (BATCH) No.	RO4929097 (80 mg)/[redacted]
DOSE / ROUTE / REGIMEN / DURATION	RO4929097 administered orally at an 80-mg dose level under fasted conditions 3 days on / 4 days off continuous treatment schedule with 21-day treatment cycles. It was expected that the recommended phase II dosing would be determined from study NO21321; however, both studies were terminated by Roche (see below for details).
REFERENCE DRUG / STROKE (BATCH) No.	Not applicable.
DOSE / ROUTE / REGIMEN / DURATION	Not applicable.
CRITERIA FOR EVALUATION	
EFFICACY:	Tumor response was evaluated according to RECIST criteria. Positron emission tomography (PET) scanning was performed to assess alterations in tumor blood flow and/or metabolic responses that might otherwise go undetected using RECIST criteria alone in view of the anticipated primarily cytostatic mode of action of RO4929097.

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PHARMACOKINETICS/ PHARMACODYNAMICS:	A comprehensive PK profile was to be evaluated during the first and second cycles of RO4929097 therapy (see page 109 for details). Peripheral blood and urine samples were to be collected to assess treatment-related changes in PD parameters (see page 109 for details). For more information see the informed consent form, see page 153 .
SAFETY:	The incidence of clinical and laboratory adverse events (AEs) were reported and graded according to NCI-CTCAE criteria, version 4.0.
STATISTICAL METHODS:	[redacted], only a listing of PET scans by study medication is provided for efficacy purposes. Adverse events were reported in frequency tables overall, by intensity, and by relationship. Laboratory values were reported in shift tables and with summary statistics. Descriptive statistics were used to summarize ECG data and vital signs.

METHODOLOGY:

RO4929097 was given orally once daily under fasted conditions on a 3 days on, 4 days off continuous administration schedule, with a 21-day cycle. Treatment continued in the absence of disease progression, unacceptable toxicities or AEs, or patient withdrawal from the study. Cohort 1 was to include 12 patients, who were to receive RO4929097 80 mg/day. Cohort 2 was to include 20 patients who were to receive RO4929097 at the Phase I monotherapy recommended phase II dosing (RPTD) defined in study NO21321. The primary endpoint was the assessment of the effect of RO4929097 on tumor blood flow and tumor metabolic activity, respectively, in patients with treatment refractory stage IIIB/IV NSCLC as assessed through $H_2{}^{15}O$ PET and ^{18}FDG PET. For additional information on the methodology, see page 94 .

PROTOCOL AMENDMENTS:

The version of the protocol used for this synoptic report was NP22383 (page 61).

AUDIT CERTIFICATE:

A compliance and training visit was conducted at one investigator site. The audit certificate is provided on (page 180).

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REASON FOR STUDY TERMINATION:

Roche decided to stop patient enrollment in studies NO21321 (phase I monotherapy study) and NP22383 (this exploratory phase II study) with Gamma Secretase Inhibitor (RO4929097) [redacted]. [redacted] Therefore, patients who were receiving RO4929097 as monotherapy were allowed to continue their treatment per protocol at the discretion of the treating physician, and continued to be clinically assessed per protocol. [redacted] (page 181).

STUDY POPULATION:

Disposition of patients: A total of 7 patients were enrolled and received at least one dose of RO4929097 80 mg/day (page 11).

Premature withdrawal: Of the 7 patients enrolled in this study, 4 withdrew due to insufficient therapeutic response, 2 withdrew for refusing treatment/not cooperating, and 1 withdrew consent. None of the patients withdrew due to AEs (page 12 and page 13).

Overview of analysis populations: All 7 patients were included in the safety population. [redacted], the efficacy population was not defined and the protocol-defined efficacy analyses (with the exception of the PET scan listings) were not performed.

Demographic data: The were 4 females and 3 males, and all were white (100%). The mean age was 55.1 years (range 33-68). A summary of demographic data is presented on page 11 .

EFFICACY RESULTS:

[redacted], the efficacy analyses were not performed, except for a listing of PET scans. No consistent anti-tumor activity was observed in the PET scan listing (page 14).

PHARMACOKINETIC / PHARMACODYNAMIC RESULTS:

[redacted] the pharmacokinetic and pharmacodynamics analyses were not performed.

SAFETY RESULTS:

Extent of exposure to trial treatment: For the overall safety population (n=7), the mean total duration of treatment was 43.1 days, with a mean cumulative dose of 1277.1 mg and mean number of cycles started at 2.6. A summary of study medication administration is presented on page 16 .

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Adverse events: A total of 45 AEs were reported by all 7 patients in this study. Overall, the most common AEs (defined as occurring in ≥ 2 patients) were fatigue (6 patients), nausea (4 patients), vomiting (4 patients), cough/diarrhea (3 patients) and pyrexia/body temperature increased (3 patients). A total of 38 treatment-related AEs were reported by all 7 patients in the study. Per the investigator, the most common treatment-related AEs (defined as occurring in ≥ 2 patients) were fatigue (6 patients), nausea/vomiting (4 patients), alopecia/diarrhea/pyrexia/cough (2 patients). The summaries of AEs and treatment-related AEs are presented on page 17 and page 20 . A glossary of preferred terms for AEs is provided on page 23 .

There were no related Grade 4 or Grade 5 events reported in this study. Three patients experienced Grade 3 events:

- Patient [redacted] experienced Grade 3 anemia on Day 15 of the study. Per the investigator, the event was unresolved and probably related to study medication.
- Patient [redacted] experienced Grade 3 aphasia and ataxia on Day 53 of the study. Per the investigator, the events were considered remotely related to study medication, as the patient suffered from ataxia caused by brain metastasis prior to start of study. These events were considered unresolved.
- Patient [redacted] experienced Grade 3 muscular weakness on Day 39 of the study. Per the investigator, the event was unresolved and remotely related to study medication.

All other events were Grade 1 or 2. A listing of patients with AEs and CTC grade is provided on page 25 .

Deaths: No deaths occurred during this study (page 28).

SAEs: A total of 2 patients reported 2 SAEs (page 29). One patient [redacted] experienced a Grade 2 SAE of nausea on Day 4 of the study. Per the investigator, this SAE resolved without sequelae and was considered probably related to study medication. Another patient [redacted] experienced a Grade 2 SAE of pyrexia (fever) on Day 6 of the study. The investigator initially suspected that the fever was due to a bronchial infection. However, since a foci was never identified for infection, the SAE was considered to be a tumor-related fever or a side effect of study medication (possibly related). The event resolved without sequelae. A listing of patients with SAEs and CTC grade is provided on page 30 . Narratives for these 2 patients are included in this report.

Premature withdrawals due to AEs: No premature withdrawals due to AEs occurred during this study (page 13).

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Laboratory parameters: Per NCI-CTC grading, all of the laboratory values were Grade ≤ 2, with the exception of Grade 3 low lymphocytes (2 patients), Grade 3 low phosphate (2 patients), Grade 3 low neutrophils (1 patient), Grade 3 low hemoglobin (1 patient), and Grade 3 low white blood cells (1 patient) (page 36).The most frequent marked laboratory abnormality was a reduction in hematocrit, which occurred in 5 patients. Findings also included high and low white blood cells in one patient and low red blood cells in one patient (page 31). None of these results were considered clinically relevant by the investigator.

ECGs and vital signs: Overall, no clinically relevant changes from baseline were observed for the ECG parameters or the vital sign measurements (page 46 and page 53).

CONCLUSIONS:

RO4929097 was safe and well tolerated when administered at 80 mg/day in this small study population. However, based on the limited data from the PET scans, no consistent anti-tumor activity was observed.