SYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL NO21895)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	**Synopsis Clinical Study Report**: Study NO21895 - RO5126766: Open-label, multicenter, dose-escalation Phase I with extension study to evaluate safety, pharmacokinetics and activity of RO5126766, a dual Raf and MEK inhibitor, administered orally as monotherapy in patients with advanced tumors. Report No. [redacted] May 2012. [redacted].
INVESTIGATORS / CENTERS AND COUNTRIES	**Three centers and investigators in 3 countries:** [redacted] Spain [redacted] United Kingdom [redacted] France **Ethics Committees Actions:** United Kingdom: [redacted] France: [redacted] Spain: [redacted] There were 4 protocol amendments. The protocol amendments are appended on page 1981.

PUBLICATIONS (REFERENCES)	1. Ishii N, Harada N, Joseph EW, et al. A novel allosteric MEK inhibitor, CH5126766 (RO5126766) suppresses RAF-mediated feedback induction of MEK phosphorylation. *Submitted to Nature Chemical Biology 2011*. 2. Martinez Garcia M, Banerji U, Albanell J, et al. First-in-human, safety, pharmacodynamic (PD) and pharmacokinetic (PK) trial of a first-in-class dual RAF/MEK inhibitor, RO5126766, in patients with advanced or metastatic solid tumor. Presented at the 8th International Symposium on Targeted Anticancer Therapies, Bethesda, Maryland; 2010 March 4-6. 3. Martinez-Garcia M, Banerji U, Albanell J, et al. First-in-human, phase I, dose-escalation study of the safety, pharmacokinetics and pharmacodynamics of RO5126766 (CH5126766), a first-in-class dual MEK/RAF inhibitor, in patients with advanced or metastatic solid tumours. *Submitted to Clinical Cancer Research Journal March, 2012*. 4. Soria JC, Banerji U, Bhaleda R, et al. First-in-human, safety, pharmacodynamic (PD) and pharmacokinetic (PK) trial of a first-in-class dual RAF/MEK inhibitor, RO5126766, in patients with advanced or metastatic solid tumor. Presented at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Berlin, Germany, 2010. EORTC-NCI-AACR Poster 365. 5. Dolly S, Albanell, J, Kraeber-Bodere U, et al. First-in-human, safety, pharmacodynamic (PD) and pharmacokinetic (PK) trial of a first-in-class dual RAF/MEK inhibitor, RO5126766, in patients with advanced or metastatic solid tumor. Presented at the Asco Annual Meeting, Chicago, Illinois; 2011 June 4-8. ASCO Poster 3006.		
PERIOD OF TRIAL	November 05 2008 – September 08 2011 Part I (dose escalation phase was completed) Part II (enrollment of patients for Part II was never started)	CLINICAL PHASE	I (with extension)
OBJECTIVES	**Primary Objectives**: Part I of the study (Dose Escalation): • To determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLT) of RO5126766 administered on an oral continuous daily schedule and to determine the appropriate dose(s) and regimen(s) of RO5126766 to be used in Part II Part II of the study (Expansion Cohort): • To investigate RO5126766 single agent activity in patients with metastatic or advanced solid tumor **Secondary Objectives:** • To determine the safety and tolerability profiles of RO5126766		

	• To determine the pharmacokinetics of RO5126766
	• To determine the pharmacodynamic effect of RO5126766 in tumors by extracellular signal regulated kinase phosphorylation (pERK) inhibition and positron emission tomography (PET) imaging, and in surrogate tissues with skin biopsy and peripheral blood samples
	• To explore the pharmacokinetic/pharmacodynamic relationship and relate this to any disease response obtained
	• To define a minimal biological dose (MBD) and an optimal biological dose (OBD)
	• To determine the recommended dose(s) and regimen(s) of RO5126766 to be used in Part II
	• To describe the anti-tumor activity of RO5126766 using:
	  • Objective response rate (ORR)
	  • Clinical benefit rate (CBR)
	  • Duration of response
	  • Progression free survival (PFS)

STUDY DESIGN	This was a Phase 1 with extension, open-label, multi-center study of RO5126766 as a single agent, administered orally on once daily (QD) x 28 days cycle. Based on the pharmacokinetic and pharmacodynamic data from the cohorts receiving QD oral doses, intermittent dosing was implemented to help identify the most appropriate and tolerable dose regimen(s) and in an attempt to increase the therapeutic window. The intermittent regimens that were introduced included a 4 days on/3 days off regimen and a 7 days on/7 days off regimen. The study was designed to have a dose escalation phase (Part I) and a dose expansion phase (Part II). Part I (Dose Escalation): The dose escalation phase of this study was completed. The run-in period (administration of RO5126766 as a single cohort dose followed by up to 7-day washout period to allow the characterization of pharmacokinetic and pharmacodynamic endpoints over time) and first 4-week cycle were considered the treatment intervals for determination of the DLT and MTD. Part II (Dose Expansion): Enrollment of patients into Part II was never started as the study was terminated after completion of Part I (Dose Escalation).

REASON FOR STUDY TERMINATION	[redacted] F. Hoffmann-La Roche made the decision not to commence enrollment of patients into Part II of the study [redacted] As halting enrollment into Part II of study NO21895 was not based on grounds of safety, the trial was continued until 28 days after the last patient's last dose for Part I in order to allow those patients who may be benefiting from the drug to continue treatment only as monotherapy at the discretion of the treating physician.
NUMBER OF SUBJECTS	The planned sample size for the whole trial was approximately 75 to 100 patients. Part I: Due to potential cohort expansion from 3 to 6 patients at higher doses, 30 to 40 patients were estimated to be required to determine the MTD and OBD in Part I. A total of 62 patients were screened of whom 10 patients were screen failures. Fifty-two patients were enrolled (page 54) and distributed across 13 cohorts in Part I according to an accelerated titration schedule. Part II: Approximately 60 patients (20 patients/tumor) were anticipated to be enrolled. However, no patients were actually enrolled as this study was terminated before Part II commenced.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Main criteria for inclusion of patients in Part I: • Patients ≥ 18 years of age and with life expectancy of ≥ 12 weeks; an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1; a histologically or cytologically confirmed diagnosis of cancer that was not amenable to standard therapy (ie, advanced and/or metastatic disease); adequate bone marrow, liver, and renal function, and normal calcemia and coagulation homeostasis. • Part I: Patients with any solid tumor type or histology could have been included, and patients must have had measurable (as per response evaluation criteria in solid tumors [RECIST] criteria) and/or evaluable disease (eg, cytologically or radiologically detectable disease such as ascites, peritoneal deposits, or lesions that did not fulfill RECIST criteria for measurable disease). Main criteria for inclusion of patients in Part II: • Part II: Patients with the following tumor types were to be enrolled: malignant melanoma, pancreatic cancer, or colorectal cancer. If emerging Part I data suggested that a particular tumor type or specific tumor histology might have been responsive to treatment, then this tumor type or histology would have been considered as preferred disease for inclusion. Patients must have had at least one measurable disease lesion as per RECIST criteria.

TRIAL DRUG / STROKE (BATCH) No.	RO5126766 (capsules 50 μg, 100 μg, 150 μg, and 800 μg). Batch numbers: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Oral QD doses over 28 consecutive days in 4-week cycles with a mandatory run-in dose during Part I initiated 6 to 7 days before the Cycle 1 Day 1 dose. RO5126766 was administered in multiple ascending doses as an oral capsule 2 hours after the last meal and not within 1 hour of the next meal. RO5126766 was administered as: • Once daily administration of 0.1, 0.2, 0.4, 0.8, 1.2, 1.8, 2.25, or 2.7 mg Based on the toxicity obtained from QD administration, the following intermittent dosing regimens were selected: • 2.7 or 4.0 mg 4 days on/3 days off (2.7 mg 4/3 or 4.0 mg 4/3, respectively) RO5126766 • 2.7, 4.0, or 5.0 mg 7 days on/7 days off (2.7 mg 7/7, 4.0 mg 7/7, or 5.0 mg 7/7, respectively) RO5126766
REFERENCE DRUG / STROKE (BATCH) No.	Not applicable
DOSE / ROUTE / REGIMEN / DURATION	Not applicable
CRITERIA FOR EVALUATION	
EFFICACY:	Patients with measurable and evaluable disease had assessments according to RECIST criteria. Tumor assessments were performed following every 2 cycles of study treatments (total of approximately 8 weeks).
PHARMACOKINETICS/PHARMACODYNAMICS:	Part I: Assessments of pharmacokinetic samples for drug concentration were performed during the run-in period, on Day 15 of Cycle 1 and Day 1 of Cycle 2. Troughs of the pharmacokinetic profile were assessed on Day 8 and Day 22 of Cycle 1. Exploratory analyses of the drug metabolite were planned but were not performed due to termination of the study. The following pharmacodynamic assessments were carried out for study NO21895: Pharmacodynamic blood samples were performed during the run-in period and on Day 15 of Cycle 1. Tumor and skin biopsies, archival tumor samples, and PET sampling were assessed. Part II: The following pharmacokinetic and pharmacodynamic assessments were planned but not implemented: • Full pharmacokinetic samplings on Day 1 and Day 15 of Cycle 1 and Day 1 of Cycle 3 (Day 57) • Pharmacodynamic blood samples on Day 1 and Day 15 of Cycle 1 Other pharmacodynamic assessments that were planned included an assessment of tumor and skin biopsies, archival tumor samples, and PET imaging.

SAFETY/EFFICACY:	Clinical safety/efficacy/biomarkers assessments included physical examinations; vital signs; ECOG performance status; weight; 12-lead electrocardiogram (ECG); ophthalmological examination; echocardiogram or multiple acquisition scan; bone scans; tumor assessment; tumor markers (if applicable); concomitant medication; adverse events (AEs); ^{18}[F]-fluorodeoxyglucose PET (if applicable); and hematology; biochemistry, and urinalysis assessments. In addition, tumor biopsy specimens of the solid tumor were obtained, pregnancy tests were conducted for all females of childbearing potential, and diabetic patients were monitored for glycemic parameters. All safety parameters were summarized using descriptive statistics and presented in tables for the safety population (all patients with at least 1 dose of study medication and with at least 1 post-baseline safety assessment). Adverse event definitions were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 3.0) [1].
STATISTICAL METHODS:	A brief description of the statistical methods follows below: Adverse events were reported in frequency tables overall, by intensity, and by relationship. Laboratory variables were reported using descriptive statistics. All AEs and abnormal laboratory variables were assessed according to the NCI-CTCAE grading system (Version 3.0) [1]. A statistical analysis was conducted at the end of the dose escalation phase (Part I) to determine the MTD, the OBD, and the most appropriate dose(s) and regimen(s) for administration during Part II of the study. Pharmacokinetic assessments of the area under the curve, clearance, volume of distribution at steady state, maximum plasma concentration, time to reach maximum plasma concentration, and the terminal half-life were performed in all patients at specified time points for each cohort. As no patients were enrolled in Part II of the study, statistical analyses for Part II were not conducted. Planned statistical analyses for Part II of the study included analyses of safety, tolerability, and anti-tumor activity. The ORR, CBR, median PFS, and duration of response were planned to be calculated for the MTD and/or OBD to evaluate the most likely effective dose for all tumor types combined and by tumor type.

METHODOLOGY:

Full details on the study methodology are presented in the schedule of assessments and procedures (page 2001 and page 2015).

This open-label, Phase 1, 2-part study of RO5126766 administered orally as a single agent on a continuous daily dosing schedule was designed to include a dose escalation phase (Part I) and a dose expansion phase (Part II). Patients enrolled in the study completed the dose escalation phase (Part I). However, enrollment of patients into the expansion phase (Part II) of the study never commenced as F. Hoffmann-La Roche terminated the study [redacted]. The study design for Part II is briefly described below.

Part I (Dose Escalation)

Six or 7 days prior to Cycle 1 of Part I, RO5126766 was administered as a single-cohort dose (run-in dose) followed by a washout period of up to 7 days. Each patient stayed in the hospital under close supervision of hospital staff for 12 hours following administration of the first dose. Not more than 1 patient per day started treatment at 1 site.

Initial dose escalation was performed in patients receiving oral RO5126766 QD (starting on Day 1) as a single agent, administered orally QD over 28 consecutive days, in 4-week cycles. Further dose escalation was performed using two intermittent schedules, (1) 4 days on followed by 3 days off and (2) 7 days on followed by 7 days off.

An accelerated titration design was used with the starting dose selected of 0.1 mg, which provided a 9.6-fold safety factor over the highest equivalent dose tolerated in monkeys [2]. The run-in phase and the first cycle (4 weeks) of treatment were considered the DLT and MTD determining periods.

One patient per dose level was enrolled at the starting dose level. If no DLT or no Grade 2 toxicity or non-DLT Grade 3 related toxicity was observed during the first cycle at a given dose level, the dose was escalated and 1 patient was enrolled in the next higher dose level. If a Grade 2 toxicity or non-DLT Grade 3 toxicity occurred at a given dose level, thereafter in the next dose level cohorts, a total of 3 patients per dose level were enrolled.

If a DLT occurred at a given dose level (dose cohorts with 1 or 3 patients), this dose level was expanded to 6 patients. If none of the other patients in the 6 patient-cohort developed a DLT, then dose escalation proceeded to the next higher dose level. The next dose level cohorts consisted of 3 new patients.

If $\geq$2 patients in a given dose level (dose cohorts with 3 to 6 patients) developed a DLT, further dose escalation to a higher dose level was stopped. The preceding dose level cohort was expanded to 6 patients, if this had not already occurred, to confirm the MTD (defined as the highest dose level at which no more than 1 out of 6 patients experienced a DLT) and evaluate associated pharmacokinetic and pharmacodynamic assessments before initiation of Part II. An intermediate dose level could have been explored after approval from the Sponsor.

Based on the evaluation of toxicity following QD administration and following the rules of the accelerated titration design, the following intermittent regimens were selected for investigation: (1) 2.7 mg 4/3 or 4.0 mg 4/3 RO5126766 and (2) 2.7 mg 7/7, 4.0 mg 7/7, or 5.0 mg 7/7 RO5126766.

Part II (Dose Expansion)

Part II of this study never commenced as the Sponsor terminated the study [redacted] It was planned that Part II would be initiated once the best dose(s) and regimen(s) were selected from Part I. Patients with 1 of 3 selected tumor types (malignant melanoma, pancreatic cancer, and colorectal cancer) would have been eligible to enroll in Part II, with each tumor type in a separate arm.

Disposition of Patients

Part I: A total of 52 patients were enrolled in Part I of study NO21895 (page 54). In the QD dosing regimen, 1 patient was enrolled to each of the following treatment groups; RO5126766 0.1 mg QD, 0.2 mg QD, and 0.4 mg QD; 3 patients were enrolled to each of the following treatment groups; RO5126766 0.8 mg QD, 1.2 mg QD, and 2.7 mg QD; 7 patients were enrolled to the RO5126766 1.8 mg QD treatment group; and 6 patients were enrolled to the RO5126766 2.25 mg QD treatment group.

In the 4 days on/3 days off dosing regimen, 7 patients were enrolled to the RO5126766 2.7 mg 4/3 treatment group and 6 patients were enrolled to the RO5126766 4.0 mg 4/3 treatment group.

In the 7 days on/7 days off dosing regimen, 6 patients were enrolled to each of the following treatment groups; RO5126766 2.7 mg 7/7 and 4.0 mg 7/7 treatment groups and 2 patients were enrolled to the RO5126766 5.0 mg 7/7 treatment group.

Part II: The study was terminated following completion of Part I. Enrollment of patients to the extension component of this study was not started.

Premature Withdrawal

All 52 patients were withdrawn from Part I of the study. Most patients (42/52, 81%) withdrew due to progression of disease (page 981). Six patients (12%) had 1 AE of either retinal detachment, blood albumin increased, pneumonitis, myopathy, left ventricular dysfunction, or spinal cord compression, and were prematurely withdrawn from the study. Four patients (8%) were withdrawn due to either refusal of treatment, insufficient therapeutic response, or administrative/other based on the amount of toxicity and alternative cancer treatment option (Table 1). Listings of patients withdrawn for AEs by analysis group and patient number are included on page 994.

Table 1 Patient Withdrawal (All-Patient Population)

Reason for Withdrawal	N = 52 No. (%)
Safety	
Adverse event	6 (12)
Non-Safety	
Insufficient therapeutic response	1 (2)
Refused treatment/did not cooperate	2 (4)
Progression of disease	42 (81)
Admin/Other (clinical decision based on amount of toxicity and alternative cancer treatment option)	1 (2)

N, total number of patients; No.,number of patients reported

Source: page 981.

Overview of Analysis Populations

Safety and pharmacokinetic analyses were performed on the all-patient population. The all-patient population included all 52 patients enrolled in the study.

Demographic Data

The majority of patients enrolled in this study were male (30 patients, 58%)(Table 2). The mean (standard deviation) age was 49.6 (12) years and patients' age ranged between 24 to 74 years across treatment groups. All patients enrolled in the study were non-Hispanic and most patients were white (49 patients, 94%) (page 54 and page 1006).

Baseline Characteristics

Patients enrolled in the study had the following tumor diagnoses: 21 patients (40%) with a diagnosis of melanoma, 10 patients (19%) with a diagnosis of colorectal cancer, 6 (12%) patients with a diagnosis of ovarian cancer, 2 patients (4%) with a diagnosis of lung cancer, 2 patients (4%) with a diagnosis of pancreatic cancer, 2 patients (4%) with cancer of the uterus, 2 patients with breast cancer (4%), 2 patients (4%) with adrenal gland cancer, and 1 patient (2%) each with a diagnosis of esophageal, testicular, cutaneous epidermoid carcinoma, pleural mesothelium, and Ewing's sarcoma (Table 2) (page 1008).

Table 2 Patient Demographics and Clinical Characteristics

Characteristic	Total Patients (N = 52)
Sex (n, %)	
Male	30 (58)
Female	22 (42)
Age, years	
Mean (SD)	49.6 (12.1)
Median	52
Range	24-74
Weight (kg)	
Mean (SD)	77.5 (18.2)
Median	74.5
Range	43.0-128.0
Ethnicity (n, %)	
Non-Hispanic	52 (100)
Race (n, %)	
White	49 (94)
Asian	2 (4)
Other	1 (2)
Baseline ECOG performance status (n, %)	
0	23 (44)
1	29 (56)
Prior anti-cancer therapies, median range	3 (1-11)
Primary tumor site and mutational status	
Melanoma	21
Colon/large intestine and rectum	10
Ovarian	6
Lung	2
Pancreas	2
Uterus	2
Breast	2

Table 2 Patient Demographics and Clinical Characteristics (cont.)

Characteristic	Total Patients (N = 52)
Esophagus	1
Adrenal gland	2
Pleural mesothelium	1
Testicular	1
Ewing's sarcoma	1
Cutaneous epidermoid carcinoma	1

ECOG, Eastern Cooperative Oncology Group; n, number of patients contributing to summary statistic; N, total number of patients; SD, standard deviation.
Source: page 1006, page 1008, and page 54 .

Concomitant Diseases and Treatments

Common concomitant diseases reported in ≥ 10% of patients included anemia (10/52 patients, 19%), hypertension (8/52 patients, 15%), abdominal pain upper (7/52, 13%), fatigue (6/52 patients, 12%), and anxiety (5/52, 10%) (page 1010). Listings of previous concomitant cancer treatments and other concomitant treatments are provided in (page 1023 and page 1084). Glossaries of the diseases and treatments are included on page 2102 and page 2108.

SAFETY RESULTS:

Primary Objective

The primary objective of Part I of the study was to determine the DLT and MTD of RO5126766. A total of 10 DLTs were observed across the 13 cohorts. Two patients experienced one DLT at the 2.7-mg QD dose level (creatine phosphokinase elevation [Grade 3] or blurred vision [Grade 3]). When the lower 1.8-mg QD dose level was expanded (7 patients total), 1 patient experienced a DLT of transaminitis (Grade 3). The dose was then escalated to 2.25 mg QD and 1 patient had a DLT of creatine phosphokinase elevation (Grade 3) (Table 3); see Roche Investigator's Brochure Fourth Version Section 5.4.1.1 [2].

Table 3 Adverse Events Characterized as Dose-Limiting Toxicities (Once Daily Regimens)

	1.8 mg QD	2.7 mg QD	2.25 mg QD
	N = 7	N = 3	N = 6
Dose-Limiting Toxicity	n (Grade)	n (Grade)	n (Grade)
Transaminitis	1 (3)		
Blurred vision		1 (3)	
Creatine phosphokinase elevation		1 (3)	1 (3)

n, number of patients; N, number of patients in the treatment group; QD, once daily.
Source: Roche Investigator's Brochure RO5126776 Fourth Version Section 5.4.1.1.

For the 4/3 regimen, patients received an initial dose of 2.7 mg with subsequent escalation to 4.0 mg. One patient experienced a DLT of blurred vision (Grade 3) at the 4.0-mg dose level (Table 4). No additional patients experienced a DLT at the 4.0-mg dose level when the cohort was expanded to 7 patients. No subsequent escalation was performed on this 4/3 regimen due to early onset (before Day 4) of 2 DLTs observed in the 7/7 dosing regimen at 5.0 mg.

For the 7/7 dose regimen, 5 patients experienced a DLT. One patient experienced a DLT of capillary leak syndrome (Grade 3) at the starting dose of 2.7 mg (Table 4), 2 patients experienced a DLT at 4.0 mg (creatine phosphokinase elevation [Grade 3] or febrile neutropenia associated with thrombocytopenia [Grade 3]), and 2 patients at the 5.0-mg dose had a DLT of blurred vision (Grade 3) or serous retinal detachment (Grade 2) see Roche Investigator's Brochure Fourth Version Section 5.4.1.1 [3].

The MTDs for the QD, 4/3, and 7/7 schedules were determined to be 2.25 mg, 4.0 mg, and 2.7 mg, respectively.

Table 4 Adverse Events Characterized as Dose-Limiting Toxicities (Intermittent Regimens)

	2.7 mg 4/3	4.0 mg 4/3	2.7 mg 7/7	4.0 mg 7/7	5.0 mg 7/7
	N = 7	N = 6	N = 6	N = 6	N = 2
Dose-Limiting Toxicity	n (Grade)	n (Grade)	n (Grade)	n (Grade)	n (Grade)
Blurred vision		1 (3)			1 (3)
Creatine phosphokinase elevation				1 (3)	
Serous retinal detachment					1 (2)
Febrile neutropenia with thromocytopenia				1 (3)	
Capillary leak syndrome			1 (3)		

n, number of patients; N, number of patients in the treatment group; QD, once daily.

Source: Roche Investigator's Brochure RO5126776 Fourth Version Section 5.4.1.1.

Adverse Events

A total of 720 AEs were reported for the all-patient population (including patients in all regimens) with each patient experiencing at least 1 AE throughout the study treatment period (page 60). The majority of AEs were assessed as related to treatment (416/720 AEs, 58%) (page 90). Overall, most AEs were of Grade 1 (440/720, 61%) or Grade 2 (205/720, 28%) intensity (page 151). Glossaries of the original terms specific to this study, with the corresponding preferred term, are included on page 2090. Listings of patients with AEs with actually received treatment are included on page 1108.

A total of 417 AEs were commonly reported AEs (incidence rate at least 10%). Most commonly reported AEs were of Grade 1 (243/417, 58%) or Grade 2 intensity (125/417, 30%). The most commonly reported AEs were dermatitis acneiform and rash (35/52 patients, 67%), diarrhea (34/52 patients, 65%), blood creatine phosphokinase increased (30/52 patients, 58%), asthenia (24/52 patients, 46%), and edema peripheral (21/52 patients, 40%). Commonly reported AEs were observed in patients across the treatment cohorts (Table 5).

Table 5 Summary of Adverse Events With Incidence Rate of at Least 10% by Body System

Body System Adverse Event	N = 52 No. (%)	Grade 1	Grade 2	Grade 3	Grade 4
General Disorders and Administration Site Conditions					
Asthenia	24 (46)	10	13	1	-
Oedema peripheral	21 (40)	14	6	1	-
Pyrexia	13 (25)	11	2	-	-
Mucosal inflammation	10 (19)	4	6	-	-
Fatigue	8 (15)	-	6	2	-
Gastrointestinal Disorders					
Diarrhoea	34 (65)	26	8	-	-
Nausea	20 (38)	18	2	-	-
Constipation	17 (33)	17	-	-	-
Vomiting	15 (29)	14	1	-	-
Stomatitis	14 (27)	7	7	-	-
Abdominal pain upper	6 (12)	4	2	-	-
Dry mouth	6 (12)	5	1	-	-
Skin and Subcutaneous Tissue Disorders					
Dermatitis acneiform and rash	35 (67)	6	16	13	-
Investigations					
Blood creatine phosphokinase increased	30 (58)	8	15	6	1
Aspartate aminotransferase increased	14 (27)	9	-	5	-
Alanine aminotransferase increased	11 (21)	7	2	2	-
Blood lactate dehydrogenase increased	9 (17)	3	2	4	-
Blood albumin decreased	6 (12)	3	2	1	-
Eye Disorders					
Vision blurred	19 (37)	13	3	3	-
Eyelid oedema	10 (19)	10	-	-	-
Macular oedema	7 (13)	4	3	-	-
Infections and Infestations					
Paronychia	11 (21)	5	4	2	-
Folliculitis	10 (19)	2	5	3	-

Table 5 Summary of Adverse Events With Incidence Rate of at Least 10% by Body System (cont.)

Body System Adverse Event	N = 52 No. (%)	Grade 1	Grade 2	Grade 3	Grade 4
Metabolism and Nutrition Disorders					
Decreased appetite	15 (29)	12	3		-
Hypoalbuminaemia	12 (23)	5	5	2	-
Hypokalaemia	7 (13)	5	-	2	-
Musculoskeletal and Connective Tissue Disorders					
Myalgia	7 (13)	7	-	-	-
Respiratory, Thoracic and Mediastinal Disorders					
Dyspnoea	8 (15)	7	1	-	-
Cough	7 (13)	6	1	-	-
Blood and Lymphatic System Disorders					
Anaemia	11 (21)	1	9	1	-

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; No., number of adverse events.

Investigator text of Adverse Events encoded using MedDRA version 14.0. Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.

Source: page 151 and page 212.

Adverse Events Leading to Withdrawal

Six patients (12%) were prematurely withdrawn from the study due to 1 AE each (myopathy, blood albumin decreased, retinal detachment, left ventricular dysfunction, pneumonitis, and spinal cord compression. Three of 6 AEs were serious adverse events (SAEs) and 5 of 6 AEs (83%) were related to study treatment (page 994). Listings of treatments for AEs are provided on page 1299.

Serious Adverse Events

Twenty-four SAEs were reported in 18 patients, including 18 SAEs that were assessed by the investigator as related to study treatment (page 214 and page 229). The majority of SAEs reported were of Grade 3 intensity. Two SAEs were of Grade 4 intensity (acute myocardial infarction and pulmonary embolism) in patients receiving 0.1 mg QD and 1.8 mg QD, respectively. An SAE of rash was experienced by 4 patients, cellulitis was experienced by 3 patients, and blood creatine phosphokinase elevation was experienced by 3 patients. All other SAEs were experienced by 1 patient. Patients receiving a dose of 2.7 mg QD experienced the most SAEs (7/24, 29%) (Table 6). Patient safety narratives for SAEs including 2 narratives for patients who experienced a DLT that were not reported as SAEs, are provided in Appendix 1.

Table 6 Summary of Serious Adverse Events by Body System, Analysis Group, and Relatedness to Treatment

Adverse Event	0.1 mg QD N = 1 No. (Y/N) G	0.8 mg QD N = 3 No. (Y/N) G	1.2 mg QD N = 3 No. (Y/N) G	1.8 mg QD N = 7 No. (Y/N) G	2.7 mg QD N = 3 No. (Y/N) G	2.25 mg QD N = 6 No. (Y/N) G	2.7 mg 4/3 N = 7 No. (Y/N) G	2.7 mg 7/7 N = 6 No. (Y/N) G	4.0 mg 4/3 N = 6 No. (Y/N) G	4.0 mg 7/7 N = 6 No. (Y/N) G	5.0 mg 7/7 N = 2 No. (Y/N) G
Cellulitis	1 (N) 3			1 (N) 2						1 (Y) 3	
Erysipelas					1 (N) 3						
Blood creatine phosphokinase increased					1 (Y) 3	1 (Y) 3				1 (Y) 3	
Troponin increased									1 (Y) 3		
Rash			1 (Y) 3		2 (Y) 3	1 (Y) 3					
Acute myocardial infarction	1 (N) 4										
Left ventricular dysfunction					1 (Y) 2						
Retinal detachment											1 (Y) 2
Vision blurred					1 (Y) 3						
Febrile neutropenia										1 (Y) 3	
Diarrhoea					1 (Y) 2						
Pyrexia							1 (N) 1				
Myopathy						1 (Y) 3					
Confusional state											1 (Y) 2
Proteinuria		1 (N) 3									
Pulmonary embolism				1 (Y) 4							
Capillary leak syndrome								1 (Y) 3			

G, grade; N, number of patients in the treatment group; No., number of events; QD, once daily; MedDRA, Medical Dictionary for Regulatory Activities.

Investigator text for adverse events encoded using MedDRA version 14.0. Only the closest relationship to treatment is counted for multiple occurrences of the same adverse event in one individual.

Source: page 214 and page 229.

Deaths

Seven deaths were reported in study NO21895. All cases of deaths were related to the progression of the disease. None were deemed by the investigator as related to trial treatment (page 1371).

Vital Signs

The standard reference ranges were 100 beats per minute (bpm) for high pulse rate and 40 bpm for low pulse rate; 90 and 140 mm Hg for low and high systolic blood pressure, respectively; and 50 and 90 mm Hg for low and high diastolic blood pressure, respectively. There was no apparent pattern of clinically significant changes in vital signs at any of the doses investigated (page 244).

Overall, there were several observations of abnormal high pulse (18/52 patients, 35%), high systolic blood pressure (24/52 patients, 46%), high diastolic blood pressure (19/52 patients, 37%), and high temperature (4/52 patients, 8%). Abnormal low measurements in the aforementioned parameters were also observed, albeit not as frequently. Patient vital signs and change from baseline (screening) are provided in the listing on page 1372.

Laboratory Assessments

Laboratory results were generally within the standard reference range for most parameters and for most patients apart from blood creatine phosphokinase elevation reported as DLTs and/or SAEs in previous sections. There were sporadic out-of-range and marked abnormalities observed for some laboratory parameters. However, there was no apparent pattern of clinically significant laboratory values at any of the doses investigated (apart from blood creatine phosphokinase elevation) (page 248).

ECG and QTc Analyses

An analysis of the maximum post-baseline QT interval corrected by Bazett's formula (QTcB) was conducted by analysis group and indicated no pattern of clinically significant changes based on dose. Eleven of 43 patients (26%) had a post-baseline QTcB interval > 450 ms; 7 patients (16%) exhibited a QTcB interval > 450 to 480 ms, 3 patients (7%) exhibited a QTcB interval > 480 to 500 ms, and 1 patient (2%) exhibited a QTcB interval > 500 ms (page 968). Listings of the QTcB data with change from baseline by patient are provided on page 1435.

Similarly, an analysis of the maximum post-baseline QT interval corrected by Fridericia's formula (QTcF) was conducted by analysis group and indicated no pattern of clinically significant changes based on dose. Five of 43 patients (12%) had a post-baseline QTcF interval > 450 ms; 4 patients (9%) exhibited a QTcF interval > 450 to 480 ms, none of the patients exhibited a QTcF interval > 480 to 500 ms, and 1 patient (2%) exhibited a QTcF interval > 500 ms (page 971). Listings of the QTcF data with change from baseline by patient are provided on page 1510.

Listings of the change from baseline for QTcB and QTcF data are on page 1585 and page 1660.

Patient ECG and individual T-, and U- wave results and listing of ECG data with change from baseline are provided on page 1735 and page 1789.

Data for ECG in MACRO/Oracle Clinical (OC) database is correct with respect to Date/Time/Visit, and Window. However, the programming derivation in the OC Database inadvertently pulled in the incorrect sample collection data for some values in the "vs" dataset, which affected some of the dates of outputs (page 1735, page 1789, page 1585, and page 1660).

EFFICACY RESULTS:

A total of 46 patients were evaluable for efficacy. There was 1 partial responder in each dosing regimen (Table 7). The 3 partial responses occurred in patients with skin melanoma (page 974, page 975, and page 1008). In total, 19 of 46 patients (41.3%) across the treatment groups achieved disease stabilization.

Table 7 Summary of Best Responses in Patients by Dosing Regimen

Summary of Best Responses in patients by Regimen
Protocol: NO21895
Analysis: All Patients

	QD (N=22)	4 On/3 Off (N=12)	7 On/7 Off (N=12)	TOTAL (N=46)
PR	1 (4.5%)	1 (8.3%)	1 (8.3%)	3 (6.5%)
SD	10 (45.5%)	5 (41.7%)	4 (33.3%)	19 (41.3%)
PD	11 (50%)	6 (50%)	7 (58.3%)	24 (52.2%)

PHARMACODYNAMIC RESULTS:

Not applicable for this Synopsis report as the study was terminated.

PHARMACOKINETIC RESULTS:

Pharmacokinetic samples were collected during the study as defined in the protocol. The drug concentrations for individual patients at each scheduled time and visit are provided in the listing (page 1931. The descriptive statistic summary for the drug concentration, including number, mean, SD, maximum, median, and minimum for each cohort at each scheduled time and visit, is provided in the listing (page 1968). Raw data are available in the bioanalytical report (page 2134).

CONCLUSIONS:

- MTD was defined as 2.25 mg, 4.0 mg, and 2.7 mg on the QD, 4 days on/3 day off, and 7 days on/7 days off dosing regimens, respectively. Based on observed DLTs, MTDs, safety, pharmacokinetic/pharmacodynamic assessments, and efficacy, the recommened phase 2 dose was defined as 2.7 mg (4 days on/3 days off).
- A total of 720 AEs were reported. The most commonly reported AEs were dermatitis acneiform and rash (35/52 patients, 67%), diarrhea (34/52 patients, 65%), blood creatine phosphokinase increased (30/52 patients, 58%), asthenia (24/52 patients, 46%), and oedema peripheral (21/52 patients, 40%).
- Six patients (12%) were prematurely withdrawn from the study due to 1 AE each (myopathy, blood albumin decreased, retinal detachment, left ventricular dysfunction, pneumonitis, and spinal cord compression). Three of 6 AEs were SAEs and 5 of 6 AEs (83%) were related to study treatment.
- Twenty-four SAEs were reported by 18 patients. Eighteen of 24 SAEs were related to study treatment.
- Seven deaths occurred due to progression of disease; none were deemed by the investigator as related to study treatment.

The study was terminated prior to enrollment of Part II. [redacted].

REFERENCES:

1. National Cancer Institute Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 3.0. http://ctep.cancer.gove/protocldevelopment/electronic applications/docs/ctcaev3. pdf 2006
2. Roche data on file. 2011.
3. Roche Investigator's Brochure RO512766, Fourth Version, August 2011.