SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NH19960)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A multicenter, randomized, open-label dose finding study of RO0503821 in anemic patients with stage IIIB or IV non-small cell lung cancer receiving first line myelosuppressive chemotherapy. Research Report [redacted] July 2007		
INVESTIGATORS / CENTERS AND COUNTRIES	Multiple investigators from Australia, Austria, Belgium, China, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Poland, and Spain,		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	First Patient Randomized: June 12, 2006 Last Patient Visit: May 29, 2007	CLINICAL PHASE	II
OBJECTIVES	Primary Objectives: The primary objectives of the study are: To select an optimal starting dose of RO0503821 to be used for the phase III trials To confirm the dose modification guidelines of RO0503821 to be used for the phase III trials Secondary Objectives: To assess the safety profile of RO0503821 To study the pharmacokinetics of RO0503821 <u>Note</u>: Recruitment for the study was suspended on February 23, 2007 due to an imbalance in deaths in the RO0503821 groups compared to the darbepoetin alfa group, in agreement with the recommendation of the DSMB made at a scheduled review meeting on February 21, 2007. Subsequently, the study was terminated on March 26, 2007, again in agreement with the DSMB's recommendation at a meeting held on March 21, 2007 because the imbalance in deaths had not changed in the intervening month since enrollment was suspended.		
STUDY DESIGN	The study was an open-label, parallel, randomized (1:1:1:1), multicenter trial containing four treatment groups. Three of the treatment groups were RO0503821 administered by subcutaneous (SC) injection every three weeks at doses of 6.3 µg/kg (group 1), 9 µg/kg (group 2) and 12 µg/kg (group 3). A total of four doses of RO0503821 was to be administered. The fourth treatment group was a reference group of patients treated with darbepoetin alfa administered at either 6.75 µg/kg SC every three weeks (a total of 4 doses) or 2.25 µg/kg every week (a total of 12 doses) according to the approved local label. Randomization procedures ensured an		

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	approximately 1:1 mix of the two darbepoetin alfa administration schedules.
NUMBER OF SUBJECTS	A total sample size of 200 (ie, 50 patients per treatment group) was planned based on practical feasibility and not based on statistical power calculation. However, this study was terminated on March 26, 2007 when 153 patients had been randomized; 38 patients were randomized into each of the 3 RO0503821 treatment groups; 20 were randomized to the darbepoetin 6.75 µg/kg SC q3week group, and 19 were randomized to the 2.25 µg/kg q1w darbepoetin group.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult (18 years or older), anemic (Hb ≤11 g/dL at screening visit) patients with stage IIIB or IV NSCLC receiving first line myelosuppressive chemotherapy.
TRIAL DRUG / STROKE (BATCH) No.	RO0503821: 6.3 µg/kg: [redacted] 9 µg/kg: [redacted] 12 µg/kg: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Injectable solution of RO0503821 supplied in vials administered at a dose of 6.3 µg/kg (group 1), 9 µg/kg (group 2) and 12 µg/kg (group 3) subcutaneously every 3 weeks. A total of four doses of RO0503821 were to be administered in each treatment group.
REFERENCE DRUG / STROKE (BATCH) No.	Darbepoetin alfa: 2.25 µg/kg: [redacted] 6.75 µg/kg: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Darbepoetin alfa administered subcutaneously at either 6.75 µg/kg every three weeks (total of four doses) or 2.25 µg/kg every week (total of 12 doses) according to the approved local label
CRITERIA FOR EVALUATION	
EFFICACY:	Average Hb change from baseline during weeks 5 – 13 (all assessments on or after day 27) was the primary efficacy variable.
PHARMACODYNAMICS:	Blood samples were taken at week 1 and at week 13 visit (or last assessment). The sampling was optional and subject to a separate signature on the informed consent. These samples will be used only for research purposes to identify dynamic biomarkers that are predictive of response to RO0503821 treatment (in terms of dose response, safety and tolerability). These samples will include

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	measurements of serum hepcidin, an iron-regulating hormone, and will be stored for up to 15 years after database closure.
PHARMACOKINETICS:	Concentrations of RO0503821 in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA method). The limit of quantification (LOQ) of the assay was 150 pg/mL. RO0503821 concentrations that were reported as being below the limit of quantification (BLQ) values or were missing, were deleted from the final PK dataset for population analysis.
SAFETY:	Adverse events, safety hematology and blood chemistry (including iron) laboratory tests, anti-erythropoietin antibody testing, vital signs, and 12-lead ECGs.
STATISTICAL METHODS	Efficacy: The average value for a patient was calculated by summing the post-baseline Hb measurements (area under the curve [AUC]) from week 5 (day 27) through the last measurement based on the trapezoidal method, and dividing the sum by the total number of days within the time interval. (This AUC calculation assumes linear Hb change between measurements). The baseline value of the patient (average of all Hb values collected from screening visit to baseline visit on day 1) was then subtracted from the average of the actual value to derive the average change from baseline value. Pharmacokinetics: Sparse RO0503821 serum concentration time data collected in the study were described using non-linear mixed effect modeling. The first order absorption, first order elimination one compartment model developed with data from previous Phase II studies were used as the basis for this analysis. Potential effect of covariates (age, gender, body weight, and calculated creatinine clearance) that could influence the pharmacokinetics of RO0503821 was tested during the analysis. Race was not tested as a covariate because the number of patients in each category was not sufficient to perform a meaningful analysis: 106 Caucasians, 3 Asians, 1 North African. Safety: All safety variables were summarized using descriptive statistics. To understand the imbalance in mortality rates among treatment groups, additional analyses were performed using survival data analysis methods. All analyses included data from all randomized patients who died during the study or had at least one post-baseline hemoglobin assessment. All comparisons between treatment groups were post-hoc, and p-values and 95% confidence intervals are reported without any adjustment for multiple comparisons.

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METHODOLOGY:

All inclusion and exclusion criteria assessments were collected within 2 weeks (14 days) prior to receiving the first dose of study medication. At examination and following written informed consent, screening assessments were performed and recorded.

EFFICACY RESULTS:

The primary efficacy parameter of the average Hb change from baseline during weeks 5 – 13 (days 27 – 85 or last assessment) for the ITT population was +0.03 g/dL, +0.50 g/dL, and -0.02 g/dL in the RO0503821 6.3, 9, and 12 µg/kg dose groups, respectively, and +0.26 g/dL in the darbepoetin alfa dose group.

PHARMACODYNAMIC RESULTS: None

PHARMACOKINETIC RESULTS:

A one compartment linear PK model was sufficient to describe sparse drug concentrations. PK parameter were estimated at the following values (inter-subject variability CV): CL/F=1.22 L/d (46%), V/F=13.5 L (45%), ka=0.248 /day. In population PK analysis in anemic cancer patients receiving multiple subcutaneous doses of RO0503821, no covariate with a clinically relevant impact on dosing was identified. In addition, in order to assess the relationship of RO0503821 exposure with dose, individual AUC values at steady state were derived using "posthoc estimates" of CL/F calculated in NONMEM and the individual medians of all RO0503821 doses in a given patient shows a linear relationship between RO0503821 exposure with dose.

SAFETY RESULTS:

General: AEs occurred most often in the following body systems: general disorders and administrative site conditions (51% to 61%), gastrointestinal disorders (41% to 51%), and blood and lymphatic system (42% to 47%). There did not appear to be a dose-related trend among the RO0503821 groups or a difference between RO0503821 and darbepoetin groups, with the exception of gastrointestinal disorders (58%, 51% and 59% of patients, respectively, in the RO0503821 6.3, 9, and 12 µg/kg groups reported gastrointestinal events, compared with 41% of patients in the darbepoetin group; this difference was explained primarily by the incidence of nausea in the RO0503821 groups). The most frequently reported adverse events across all treatment groups were nausea, anorexia, decreased hemoglobin, neutropenia, vomiting, and fatigue. Despite the imbalance in deaths, the incidence of AEs, severe AEs, and SAEs were comparable across all treatment groups and within the limits expected in a population of NSCLC patients receiving myelosuppressive chemotherapy..

TVE: The incidence of TVEs was ≤13% across treatment groups (13 patients, total of 16 confirmed TVEs). There were no dose-related RO0503821 trends and no differences between RO0503821 and darbepoetin treatment groups in the incidence of TVEs. One, 4, 3, and 5 patients in the 6.3, 9, 12 µg/kg and darbepoetin alfa groups, respectively, reported at least one confirmed TVE.

Deaths: A total of 33 patients died during the study (8, 12, 9, and 4 in the RO05038216.3, 9, and 12 µg/kg and darbepoetin groups, respectively). The causes of death in all 4 arms were assessed by the Sponsor as due to comorbid illnesses and cytotoxic effects of chemotherapy in about 50% of the cases, and progressive lung cancer in about 50% of the cases (2/8 [25%], 6/12 [50%], and 5/9 [56%] in the RO05038216.3, 9, and 12 µg/kg groups, respectively, and 2/4 [50%] in the darbepoetin alfa dose group). Most events leading to death and most deaths were associated with low (not high) Hb levels.

A multivariate Cox regression analysis performed for patients treated with RO0503821 using the actual total RO0503821 dose administered during the study (µg/kg/q3wk) had a hazard ratio (95% CI) of 1.01 (0.89-1.13), indicating that there was no association of RO0503821 doses with risk of death. After adjusting for potential risk factors a multivariate Cox regression analysis showed the hazard ratio (and 95%

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CI) of death in each RO0503821 dose group (6.3, 9, and 12 µg/kg) relative to the darbepoetin alfa group as 2.72 (0.78-9.52), 4.00 (1.24-12.96), and 2.38 (0.71-7.99). A similar analysis of all RO0503821 groups combined showed the hazard ratio of death (and 95% CI) for RO0503821 relative to darbepoetin alfa as 2.97 (1.01-8.71), indicating a statistically significant treatment difference and that mortality differences between RO0503821 and darbepoetin are not a result of the RO0503821 patients being at higher risk.
SAEs: Across all treatment groups, 50%, 62%, and 45% of patients in the RO0503821 6.3, 9, and 12 µg/kg groups, respectively, and 59% of patients in the darbepoetin alfa group experienced SAEs. Overall, there was no evidence of a dose-related trend in RO0503821 groups for any of the SAEs.
Withdrawals: A total of 19, 18, and 16 patients randomized to receive RO0503821 6.3, 9, and 12 µg/kg dose groups, respectively, withdrew from the study prior to the termination of the trial. Fifteen patients in the darbepoetin alfa group withdrew prematurely. A total of 5 patients (one each in the RO0503821 6.3 and 9 µg/kg groups and 3 in the darbepoetin alfa group) were prematurely withdrawn because of an adverse event.

CONCLUSIONS:

1) There was an imbalance in the rate of all cause mortality during the study (ie, within 28 days from the last dose of study medication) among the 4 treatment groups, with the highest rate seen in the RO0503821 9 µg/kg dose group.
2) The deaths were not associated with a hemoglobin >13 g/dL or hemoglobin rate of rise (>1.5 g/dL during 3-weeks interval).
3) No dose-response relationship in all-cause mortality was observed with the RO0503821 doses actually administered.
4) Disease progression represented approximately 50% of the causes of deaths in all treatment groups, with no dose-response relationship observed in RO0503821 dose groups.
5) There was an imbalance in clinically relevant baseline characteristics among the 4 treatment groups, including: a shorter time from diagnosis to the start of study in the darbepoetin group, more ECOG 0 in the darbepoetin alfa group versus more ECOG 1 in the RO0503821 groups, more patients with metastases to liver in the RO0503821 9 µg/kg group and metastases to lung in RO0503821 12 µg/kg group, fewer respiratory disorders (eg, chronic obstructive pulmonary disease) at baseline in the darbepoetin alfa group, and more patients in the darbepoetin alfa group with large-cell lung carcinoma compared with more patients in the RO0503821 6.3 and 9 µg/kg groups with lung adenocarcinoma.
6) Although some imbalances were observed in select potential risk factors at baseline, the multivariate regression analyses of death or time-to-death showed higher hazard ratios in the RO0503821 groups relative to the darbepoetin alfa group after adjusting for the potential risk factors. The results should be interpreted with caution since the study was not designed to detect differences in overall survival among treatment groups and the analysis was done post-hoc without applying any adjustment for multiple comparisons. In addition, all serious adverse events, including death, were only collected for up to 28 days after the last dose. Therefore, these results represent only a limited time period during which the survival status was collected.
7) No differences were noted among the 4 treatment groups in regard to incidence of AEs, serious/severe AEs, or TVEs reported during study.