SYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL BH20198)

COMPANY: F. Hoffmann-La Roche	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NeoRecormon®	
NAME OF ACTIVE SUBSTANCE(S): Epoetin Beta	

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	An open-label, randomized, multicenter trial investigating the efficacy and safety of once weekly (reduced administration frequency) NeoRecormon® therapy versus thrice weekly NeoRecormon® therapy in anemic patients with metastatic solid tumors (breast, lung, colorectal, ovarian, cervical and prostate cancer) receiving chemotherapy (or scheduled to receive chemotherapy) for at least 9 weeks. Protocol BH20198 (SNOW) / Abbreviated Study Report [redacted] / August 20, 2007.		
INVESTIGATORS / CENTERS AND COUNTRIES	Multicenter study - Co-ordinating Investigator: [redacted] Germany		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	September 28, 2006 to March 7, 2007	CLINICAL PHASE	IIIb
OBJECTIVES	The primary objective of the study was to demonstrate that once-weekly (reduced administration frequency) NeoRecormon therapy is at least as effective as thrice weekly administration of NeoRecormon in anemic patients with solid tumors receiving chemotherapy. Due to the insufficient number of subjects recruited into the study as a result of the premature termination of enrollment, the primary objective could not be achieved. The primary objective of the current report was to present a descriptive analysis of hemoglobin over time and compare the safety of NeoRecormon administered 30,000 IU once weekly, sc with NeoRecormon administered 10,000 IU thrice weekly, sc.		
STUDY DESIGN	Open-label, randomized, multicenter, two arm study		
NUMBER OF SUBJECTS	45 Enrolled	No. Evaluated: Safety / Efficacy	
	Thrice Weekly Group	24 / 24	
	Once Weekly Group	21 / 21	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Anemic (Hb ≤ 11.0 g/dL), adult (≥ 18 years old) subjects with metastatic disease of histologically or cytologically documented diagnosis of solid tumors (breast cancer, NSCLC, SCLC, colorectal, ovarian, cervical and prostate cancer) receiving chemotherapy (or scheduled to receive chemotherapy) for at least 9 weeks.		
TRIAL DRUG / STROKE (BATCH) No.	NeoRecormon (epoetin beta) solution for injection in 10,000 IU, 20,000 IU or 30,000 IU pre-filled syringes / Batch nos:		

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	10,000 IU – [redacted] 20,000 IU – [redacted] 30,000 IU – [redacted]
DOSE / ROUTE / REGIMEN / DURATION	30,000 IU administered sc, once weekly for a maximum of 12 doses. 10,000 IU administered sc, thrice weekly for a maximum of 36 doses.
REFERENCE DRUG / STROKE (BATCH) No.	n/a
DOSE / ROUTE / REGIMEN / DURATION	n/a
CRITERIA FOR EVALUATION	
EFFICACY:	<u>Primary Variable</u> - Time- and baseline-adjusted Hb AUC <u>Other Variables</u> - Iron parameters over time - Iron medication and blood transfusions
SAFETY:	Adverse events, laboratory test parameters (NCI-CTC grading), vital signs.
STATISTICAL METHODS	Baseline demographic data, efficacy and safety data are summarized using descriptive statistics. Due to early termination of the study for futility reasons, no formal statistical hypothesis testing was done. Hematology (hemoglobin and hematocrit) and iron (serum iron, ferritin, calculated TSAT, TIBC, transferrin) parameters over time have been analyzed descriptively. In addition, iron medication, blood transfusions, adverse events, laboratory test parameters and vital signs data have all been summarized.

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METHODOLOGY:

Eligible subjects were randomized centrally into one of two treatment arms to begin treatment with NeoRecormon (starting dose 30,000 IU sc) either as a once weekly administration or as a thrice weekly administration (3 x 10,000 IU). Randomization was stratified by country, baseline Hb (Hb ≤ 10g/dL versus Hb >10 g/dL) and by concomitant chemotherapy (cisplatin-based chemotherapy versus other). Blood pressure, iron parameters, hematology parameters, TEEs and safety laboratory parameters were assessed at baseline and at Weeks 3, 4, 6, 9 and a final visit at Week 12. Iron therapy and transfusions were administered as required and concomitant medications and adverse events recorded on a continuous basis throughout the trial up to 15 days after last dose.

EFFICACY RESULTS:

Despite the limited sample size, the treatment groups were well balanced with regards to demographics and baseline disease characteristics. The median baseline hemoglobin level was comparable between the study arms (9.8 g/dL thrice weekly versus 10.0 g/dL once weekly).

An overview of the efficacy results in this trial is shown below. In summary, there were no noteworthy differences between the study arms with respect to mean changes from baseline in hemoglobin levels, hematocrit levels and time/baseline adjusted AUC. A comparable proportion of patients in each study arm received blood transfusions during the study, with the majority receiving one transfusion. No clinically relevant differences between the treatment groups with respect to the change from baseline to last value in any of the iron parameters assessed during the study (serum iron, TIBC, transferrin, TSAT) were seen. Overall, a higher percentage of subjects in the thrice weekly epoetin beta treatment group (75%) received iron supplementation during the trial compared with subjects in the once weekly epoetin beta treatment group (67%).

Parameter	**Thrice Weekly Epoetin Beta N=24**	**Once Weekly Epoetin Beta N=21**
Median increase from baseline to last value in Hb levels	1.8 g/dL	2.0 g/dL
Median time- and baseline-adjusted Hb AUC	1.1 g/dL	1.7 g/dL
Median hematocrit increase from baseline to last value	6.2%	5.9%
Blood transfusions	4 (17%)	3 (14%)
Iron supplementation	18 (75%)	14 (67%)

SAFETY RESULTS:

There were no clinically relevant differences in the types of adverse events between the two treatment groups, with gastrointestinal disorders being the most frequently reported adverse events during the trial (38%, 9/24 in the thrice weekly group and 29%, 6/21 in the once weekly group). Overall, the most commonly reported gastrointestinal event was nausea which was reported by 21% (5/24) of subjects in the thrice weekly group and 5% (1/21) of subjects in the once weekly group. Serious adverse events were reported by 33% (8/24) of subjects receiving thrice weekly epoetin beta and 29% (6.21) of subjects in the

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once weekly group.
One subject in the thrice weekly epoetin beta treatment group died as a result of a pulmonary hemorrhage and one subject in the once weekly epoetin beta treatment group died as a result of the underlying disease progression. Neither death was considered by the investigator to be related to trial treatment.
In addition, one subject experienced an adverse event leading to dose modification; deep vein thrombosis, however this event was not considered related to epoetin beta treatment. Three subjects reported a TEE during the course of the trial (DVT and thrombophlebitis in the thrice weekly group; CVA in the once weekly group). All three TEEs recorded by subjects during the trial were reported as serious adverse events by the investigator, however, none was considered related to epoetin beta treatment. No fatal TEEs occurred during the study.
No clinically relevant differences between the two treatment groups over time were seen with respect to laboratory parameters or vital signs.

CONCLUSIONS:

Within the limitations of the early termination of study BH20198, the results support a comparable efficacy and safety profile of a once weekly versus thrice weekly dosing regimen of epoetin beta in patients with solid tumors receiving chemotherapy within the currently approved label, with an intervention Hb level of < 11 g/dL and an upper Hb target of 13 g/dL. No new or unexpected safety findings were identified which would alter the known safety profile of epoetin beta in cancer patients with symptomatic anemia receiving chemotherapy.