2. SYNOPSIS

Name of Sponsor: Amgen, Inc.

Name of Finished Product: motesanib diphosphate (also known as motesanib or AMG 706)

Name of Active Ingredient: motesanib diphosphate

Title of Study: A Randomized Phase 2 Trial of Double-blind, Placebo-controlled AMG 706 in Combination With Paclitaxel, or Open-label Bevacizumab in Combination With Paclitaxel as First-line Therapy in Women With HER2 Negative Locally Recurrent or Metastatic Breast Cancer

Investigator(s) and Study Center(s): This study was conducted at 71 sites in 12 countries. The names of principal investigators and their affiliations are provided in Appendix 4.

Publication(s):

Martin M, Roche H, Pinter T, et al. Motesanib, or open-label bevacizumab, in combination with paclitaxel, as first line treatment for HER2-negative locally recurrent or metastatic breast cancer: a phase 2, randomized, double-blind, placebo-controlled study. *Lancet Oncol*. 2011;12:369-376.

Martin M, Hurvitz S, Kennedy J, et al. CIRG/TORI 010: First Analysis of a randomized phase II trial of motesanib plus weekly paclitaxel (P) as first line therapy in HER2-negative metastatic breast cancer (MBC). *Eur J Cancer*. 2009;7(2 Suppl):259. Abstract O-5001.

Mackey J, Hurvitz S, Crown J, et al. CIRG/TORI 010: 10-Month Analysis of a Randomized Phase II Trial of Motesanib Plus Weekly Paclitaxel as First Line therapy in HER2-Negative Metastatic Breast Cancer (MBC). *Cancer Res*. 2009;69(24 Suppl):497S-498S.

Study Period: 01 July 2006 (2 subjects under original protocol);
01 December 2006 (under amended protocol) to 08 May 2009 (data cut-off for 10-month analysis; 42 subjects still on study treatment)

Development Phase: Phase 2

Introduction and Objectives: This is a phase 2, multicenter, prospective, randomized study to determine the efficacy of motesanib in combination with paclitaxel as a double-blind, placebo-controlled comparison with paclitaxel alone. The study also includes a paclitaxel and open-label bevacizumab arm, and an optional roll-over to motesanib monotherapy following disease progression for subjects randomized to paclitaxel alone (Arm A).

The primary objective was to determine if treatment with motesanib plus paclitaxel was superior to placebo plus paclitaxel in subjects with HER2 negative locally recurrent or metastatic breast cancer based on objective response rates.

The secondary objectives were to estimate the differences in progression-free survival, clinical benefit, overall survival and duration of response between Arm A (placebo plus paclitaxel) and Arm B (motesanib plus paclitaxel). Additional secondary objectives were to estimate the difference in objective response rate, progression-free survival time, clinical benefit, overall survival and duration of response between Arm B (motesanib plus paclitaxel) and Arm C (bevacizumab plus paclitaxel), and to evaluate the safety and tolerability in the 3 treatment arms.

[redacted]

[redacted]

Methodology: This is a phase 2, multicenter, randomized study designed to determine the efficacy of motesanib in combination with paclitaxel in a double-blind, placebo-controlled comparison with paclitaxel alone. The study also includes a paclitaxel and open-label bevacizumab arm, and an optional roll-over to motesanib monotherapy following disease progression for subjects randomized to paclitaxel alone (Arm A). Prior to randomization, subjects were stratified according to prior adjuvant or neoadjuvant chemotherapy (taxane containing regimens versus other regimens versus none), number of metastatic sites (< 3 versus ≥ 3), and estrogen and/or progesterone receptor status (positive versus negative). Eligible subjects with measurable locally recurrent or metastatic breast cancer were randomized in a 1:1:1 ratio to receive paclitaxel (90 mg/m^2 intravenous [IV] over 1 hour every week for 3 weeks of each 4-week cycle) together with blinded placebo equivalent of 125 mg motesanib orally (PO) once daily (Arm A), blinded 125 mg motesanib PO (5 x 25 mg tablets) once daily (Arm B), or open-label bevacizumab 10 mg/kg IV given after paclitaxel treatment on week 1 and 3 of each 4-week cycle (Arm C). Treatment continued until disease progression, unacceptable toxicity or withdrawal of subject consent.

Plasma samples for measurement of motesanib concentration were collected prior to dosing on day 8 and day 15 of cycle 1. Plasma samples for measurement of paclitaxel concentration were collected at the end of infusion on day 1 of cycle 1 and cycle 2. [redacted]

An independent centralized committee reviewed radiological images of each subject taken approximately every 8 weeks until disease progression. Subjects randomized to paclitaxel plus placebo (Arm A) who had a documented disease progression per protocol were eligible to roll-over to treatment with open-label motesanib monotherapy. Subjects receiving paclitaxel plus placebo who received open-label motesanib monotherapy after disease progression were to undergo radiological imaging every 8 weeks until subsequent disease progression, death, unacceptable toxicity or withdrawal of subject consent.

This report details results from the primary analysis collected from 01 December 2006 (date the first subject was enrolled under protocol amendment 1) to 10 November 2008 (primary analysis data cutoff date [ie, when subjects had been on the study for at least 16 weeks]). This report also details results from the 10-month data analysis using data collected from 01 December 2006 to 08 May 2009 (data cutoff date [ie, when subjects had been on the study for at least 10 months]).

Number of Subjects Planned: 273

Number of Subjects Enrolled: 282

Sex: women, 100% (n = 282)

		Motesanib N = 91	Placebo N = 94	Bevacizumab N = 97
Age (years):	mean (SD)	55.3 (10.6)	53.0 (10.2)	55.2 (11.3)
Ethnicity (Race): n (%)	Asian	7 (7.7)	10 (10.6)	7 (7.2)
	Black	2 (2.2)	1 (1.1)	0 (0)
	Caucasian	80 (87.9)	80 (85.1)	86 (88.7)
	Hispanic	2 (2.2)	2 (2.1)	4 (4.1)
	Other	0 (0)	1 (1.1)	0 (0)

Diagnosis and Main Criteria for Eligibility: Subjects were women 18 years of age or older, with Eastern Cooperative Oncology (ECOG) Performance Status of 0 or 1, adequate organ and hematologic function, histologically or cytologically confirmed adenocarcinoma of the breast with measurable (as per modified Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.0) or locally recurrent disease not amenable to resection with curative intent or metastatic disease. Tumors (primary or metastatic) were HER2 negative by fluorescence in-situ hybridization (FISH) or chromogenic in-situ hybridization (CISH), or 0, 1+ overexpression by immunohistochemistry.

Investigational Product, Manufacturing Batch Number: Manufacturing lot numbers for motesanib were [redacted]. Manufacturing lot numbers for open-label motesanib were [redacted].

Manufacturing lot numbers for placebo were [redacted]

Duration of Treatment: Treatment was continued until disease progression per modified RECIST (Version 1.0), unacceptable toxicity or withdrawal of subject consent. Subjects randomized to placebo were eligible to receive motesanib monotherapy 125 mg once daily within 2 weeks after progression on paclitaxel plus placebo. All subjects were to be followed for survival until death or for up to 60 months following randomization, whichever is earlier. The analysis of long-term follow-up data will be covered in the final clinical study report.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Bevacizumab: 10 mg/kg IV infusion on day 1 of weeks 1 and 3 for each 4-week cycle [Arm C]. Paclitaxel: 90 mg/m^2 IV infusion over 1 hour every week for 3 weeks for each 4-week cycle.

Study Endpoints

Primary Efficacy Endpoint: Objective tumor response rate (complete response [CR] and partial response [PR]) according to modified RECIST (Version 1.0) as determined by independent centralized radiological review.

Secondary Efficacy Endpoints: Progression-free survival (PFS), duration of response, clinical benefit (incidence of CR, PR and stable disease (SD) lasting > 24 weeks), and overall survival time (OS).

Safety Endpoints: Incidence of adverse events and laboratory abnormalities

Exploratory Endpoints:

- [redacted]

Statistical Methods:

Efficacy Analysis: The efficacy analyses were conducted on the Intent-to-Treat (ITT) Analysis Set, which consisted of all subjects randomized according the new randomization list (as part of protocol amendment 1). Subjects were included in the analyses according to their randomized treatment assignment. Analyses were also conducted on the Eligible Analysis Set. The primary endpoint of objective response rate was compared between the paclitaxel plus placebo and the paclitaxel plus motesanib groups at the 0.05 level of significance.

Descriptive statistics were provided for best overall tumor response for each treatment arm. The number and proportion of subjects within each category of response (CR, PR, SD, progressive disease [PD], non-evaluable, and missing) were presented. The proportion was calculated by dividing the number of subjects within each category of response by the number of subjects available in the ITT Analysis Set. Each subject was counted within only one response group, with the best response prior to PD during the study as the classification group. Objective response rates (ORR) (PR+CR) between the paclitaxel plus placebo and the paclitaxel plus motesanib groups were compared using the stratified Cochran-Mantel-Haenszel statistic (adjusted for the stratification factors) at the 0.05 level of significance. The 2-sided 95% confidence interval (CI) was calculated for the differences in objective response rates between the paclitaxel plus placebo and the paclitaxel plus motesanib groups.

Estimates of the treatment effect of the paclitaxel plus placebo and the paclitaxel plus motesanib groups were obtained for PFS and OS. Duration of response (responders only) was summarized for each group. For each treatment arm, Kaplan-Meier (KM) curves were presented for each of the time-to-event endpoints. The KM medians (if estimable) were derived, along with their 2-sided 95% confidence intervals. Cox proportional hazards models were used to estimate the hazard ratio for comparing the paclitaxel plus placebo and the paclitaxel plus motesanib groups (adjusted for the stratification factors) and to produce the associated 95% confidence interval for all time to event endpoints.

Estimates of the difference between the paclitaxel plus bevacizumab and the paclitaxel plus motesanib groups for objective response rate and the time to event variables were provided using 2-sided 95% confidence intervals. Analyses comparing the objective response rate and PFS of paclitaxel plus bevacizumab and the paclitaxel plus placebo groups were also conducted.

The primary and secondary efficacy endpoints were summarized for the subjects in the paclitaxel plus placebo group who received subsequent motesanib monotherapy.

Pharmacokinetic Analysis: Descriptive statistics of the individual motesanib trough (C_{min}) values on days 8 and 15 of cycle 1 and paclitaxel end-of-infusion (maximal concentration; C_{max}) on day 1 of cycles 1 and 2 were summarized (means, standard deviations, median, minimums and maximums) using validated software.

Patient-reported Outcomes (PRO) Analysis: The means and standard deviations for the EQ-5D health state preference and utility score were described. Comparison of outcomes based on analysis of covariance (ANCOVA) model using the stratification factors were performed for motesanib versus placebo and for motesanib versus bevacizumab.

Safety Analysis: Adverse events were coded in the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and a preferred term, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Amgen has adopted the Council for International Organizations of Medical Sciences (CIOMS) definition of an adverse event of interest (EOI), which is “a noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.” (CIOMS VI, 2005). The following prespecified EOIs were summarized separately: diarrhea, hypertension, reversible posterior leukoencephalopathy syndrome events, cholecystitis and gallbladder perforation, thromboembolic events, left ventricular dysfunction, hypothyroidism, hemorrhagic events, gastrointestinal perforation, fistula and intra-abdominal

abscess events; proteinuria and nephrotic syndrome; impaired wound healing; pancreatitis; hepatic toxicity; hematologic events; and peripheral neuropathy. Subject incidence rates of treatment-emergent adverse events, treatment-emergent EOIs, serious adverse events, and adverse events leading to withdrawal were tabulated by system organ class and preferred term. Narratives of deaths and serious adverse events were provided.

In support of the EOI assessment of left ventricular dysfunction, echocardiogram (ECHO)/MUGA assessments were performed for predicting risk of developing cardiac dysfunction and later cardiac events in this subject population. Summary statistics for ECHO/MUGA parameters (left ventricular ejection fraction [LVEF]) were provided for baseline, patients' trough value post baseline (any cycle), and end of treatment, as well as the percentage change from baseline. The number and percentage of subjects with ejection fractions within each of the following categories was summarized for subjects' trough value post baseline (any cycle): ≥10% absolute decrease from baseline, ≥ 15% relative decrease from baseline, absolute value < 40% or ≥ 10% absolute decrease from baseline and absolute value < 40%, and ≥ 10% absolute decrease from any 2 consecutive time points. The number and percentage of subjects with any decrease (based on any of the above categories) was summarized.

Laboratory parameters were summarized at baseline and end of study (last observed value). Additionally, the maximum and minimum observed post-baseline values were summarized along with the change from baseline to the maximum observed value, minimum observed value and end of study. Tables of shifts in toxicity (CTCAE Version 3.0) from baseline for selected laboratory parameters and selected time points were also provided.

Prior to protocol amendment 1, 2 subjects ([redacted] and [redacted]) were randomized to receive either 75 mg twice daily of motesanib or placebo. These subjects were not included in the safety or efficacy analyses. No serious adverse events were reported for these 2 subjects.

Summary of Results:

For the purposes of reporting results, Arm A (paclitaxel plus blinded placebo) is referred to as the placebo arm, Arm B (paclitaxel plus blinded motesanib) is referred to as the motesanib arm, and Arm C (paclitaxel plus bevacizumab) is referred to as the bevacizumab arm.

Subject Disposition: A total 282 subjects were included in the ITT Analysis Set, including 91 subjects randomized to motesanib, 94 subjects randomized to placebo, and 97 subjects randomized to bevacizumab. Five subjects (4 allocated to the placebo arm and 1 allocated to the bevacizumab arm) did not receive placebo or bevacizumab treatment and were excluded from the safety analyses. In addition, 1 subject randomized to placebo incorrectly received motesanib for over 7 days and was re-classified for the Safety Analysis Set as active motesanib resulting in 92 subjects treated with motesanib, 89 treated with placebo, and 96 treated with bevacizumab. Of the 89 subjects treated with placebo, 13 subjects (14%) subsequently entered the roll-over portion of the study and were treated with motesanib monotherapy. The 2 subjects randomized and treated according to the original randomization list, prior to protocol amendment 1, were excluded from safety and efficacy analyses.

At the time of the 10-month analysis, 42 of the 277 subjects (15.2%) in the Safety Analysis Set were still on study treatment and 235 subjects (84.8%) completed study treatment, including 80 subjects (87.0%) treated with motesanib, 82 subjects (92.1%) treated with placebo, and 73 subjects (76.0%) treated with bevacizumab. The most common reasons for discontinuation of study treatment were disease progression (132 [47.7%]), adverse experiences (54 [19.5%]) and other (20 [7.2%]). One hundred and six subjects (37.6%) in the ITT Analysis Set completed the study, with the remaining 176 subjects (62.4%) ongoing in either study treatment or study follow-up. Of the 13 subjects in the Roll-over Analysis Set, 12 completed study treatment, with 1 having ongoing study treatment.

Efficacy Results: The primary efficacy endpoint of this study is the objective response rate according to modified RECIST (Version 1.0) as determined by independent centralized radiologic review. The primary analysis was scheduled when subjects were on the study for at least

16 weeks. Updated objective response rate results from the 10-month data analysis are also reported. For secondary endpoints (progression-free survival, duration of response, clinical benefit, and overall survival), results from the 10-month data are presented. The primary analysis set is the ITT Analysis Set for all efficacy endpoints. Analyses for these endpoints were also presented for the subjects who received open-label motesanib monotherapy during the roll-over portion of the study (Roll-over Analysis Set).

The study was powered for comparison of objective response rates between motesanib and placebo, with statistical significance deemed at a level of 0.05. The comparison between motesanib and bevacizumab is for estimation. Ad hoc analyses also compared bevacizumab and placebo. The p-values for these analyses are descriptive and no multiplicity adjustments were made.

The objective response rate was numerically higher in the subjects randomized to motesanib (48.4%; 95% CI: 37.7% to 59.1%) and bevacizumab (45.4%; 95% CI: 35.2% to 55.8%) compared with subjects randomized to placebo (35.1%; 95% CI: 25.5% to 45.6%) for the primary analysis at 16 weeks. The estimated difference in objective response rates between subjects randomized to motesanib and subjects randomized to placebo was 13.3% (95% CI: -0.8% to 27.3%); however, this difference was not statistically significant at the 0.05 level after adjustment for the stratification factors (p = 0.09). The estimated difference in objective response rate between subjects randomized to motesanib and subjects randomized to bevacizumab was 3.0% (95% CI: -11.3% to 17.3%; p = 0.72).

For the 10-month data analysis, the objective response rates were 50% in subjects randomized to motesanib, 42% in subjects randomized to placebo, and 52% in subjects randomized to bevacizumab. The estimated differences in objective response rates between subjects randomized to motesanib and subjects randomized to placebo (8.0% [95% CI: -6.4% to 22.3%; p = 0.31]) and between subjects randomized to motesanib and subjects randomized to bevacizumab (-2.1% [95% CI: -16.4% to 12.2%; p = 0.75]) were not significant. The estimated difference in objective response rate between subjects randomized to bevacizumab and subjects randomized to placebo was also not significant (p = 0.17). The objective response rate in the Roll-over Analysis Set (n = 13) was 7.7% (PR, n = 1).

Disease progression or death due to any cause occurred in 60%, 55%, and 56% of subjects randomized to motesanib, placebo, and bevacizumab, respectively, at the time of the 10-month data analysis. The adjusted hazard ratio for progression free survival was 0.92 (95% CI 0.62, 1.37) for subjects randomized to motesanib over subjects randomized to placebo, and 1.32 (95% CI 0.89, 1.98) for subjects randomized to motesanib over subjects randomized to bevacizumab. Median PFS time was longer in subjects randomized to bevacizumab (11.5 months) than subjects randomized to motesanib (9.5 months) or placebo (9.0 months).

The clinical benefit rates (the percentage of subjects who achieved CR, PR or SD lasting from randomization to > 24 weeks) were 66%, 49%, 68% in subjects randomized to motesanib, placebo, and bevacizumab, respectively. The 95% CI for the difference in clinical benefit rates between the motesanib arm and the placebo arm was 3% to 31% (p = 0.024). The 95% CI for the difference in clinical benefit rates between the motesanib and the bevacizumab arm was -16% to 11% (p = 0.69). The clinical benefit rate in the Roll-over Analysis Set (n = 13) was 15.4%.

At the time of analysis, there were insufficient data available to draw conclusions regarding overall survival; however the percentage of subjects who died was similar across the treatment arms (30%, 29%, and 28% of subjects randomized to motesanib, placebo, and bevacizumab, respectively).

Among the subjects who responded, those randomized to bevacizumab had a longer median duration of response (15.4 months) than subjects randomized to either motesanib (9.2 months) or placebo (9.5 months).

Pharmacokinetics Results: [redacted]

Patient-reported Outcome Results: Due to a substantial amount of missing data, analyses based on imputed data are described. [redacted]

Biomarker Results: [redacted]

Safety Results: For safety evaluation endpoints, results from the 10-month data summary tables are presented. Exposure to study treatment (ie, motesanib or bevacizumab) was lower in the motesanib arm than the bevacizumab arm in this study, with a mean relative dose intensity of 86.7% for motesanib-treated subjects compared with 96.9% for bevacizumab-treated subjects. In addition, subjects received motesanib for a median of 6 cycles compared with bevacizumab for a median of 9 cycles. Treatment-emergent adverse events were reported for 99% of subjects treated with motesanib, 100% of subjects treated with placebo, and 100% of subjects treated with bevacizumab. At the System Organ Class level, the incidence of adverse events was highest in the motesanib treatment arm for the following: gastrointestinal disorders, nervous system disorders, general disorders and administration site conditions, vascular disorders, metabolism and nutrition disorders, investigations, eye disorders, cardiac disorders, hepatobiliary disorders, reproductive system and breast disorders, and endocrine disorders. The most common adverse events with a higher incidence in motesanib-treated subjects than in placebo-treated subjects or bevacizumab-treated subjects included diarrhea, hypertension, nausea, abdominal pain, and vomiting. The most common adverse events with a higher incidence in bevacizumab-treated subjects than in placebo-treated subjects or motesanib-treated subjects included alopecia, peripheral sensory neuropathy, epistaxis, nail disorder, and cough.

The incidence of adverse events with a worst grade of 3, 4, or 5 was 74% in motesanib-treated subjects, 43% in placebo-treated subjects, and 68% in the bevacizumab-treated subjects.

Diarrhea, fatigue and hypertension were reported more frequently in motesanib-treated subjects compared with placebo-treated subjects and bevacizumab-treated subjects; whereas peripheral sensory neuropathy was reported more frequently in the bevacizumab-treated subjects compared with placebo-treated subjects and motesanib-treated subjects.

Fatal adverse events (occurring within 30 days of randomized study treatment) were reported for 1% of subjects treated with motesanib, 3% of subjects treated with placebo, and 1% of subjects treated with bevacizumab. In addition, 1 subject experienced a fatal adverse event during roll-over motesanib treatment (hepatic failure and hepatic encephalopathy secondary to liver metastases).

Serious adverse events were reported in 37% of subjects treated with motesanib, 29% of subjects treated with placebo, and 23% of subjects treated with bevacizumab. The most commonly reported serious adverse event for motesanib-treated subjects was abdominal pain, which occurred in 5% of subjects treated with motesanib and in 2% subjects treated with placebo. In addition, serious adverse events reported only for motesanib-treated subjects included diarrhea (4%) and cholecystitis (4%, including 1 event of chronic cholecystitis).

Overall, 30%, 13%, and 23% of subjects treated with motesanib, placebo, and bevacizumab, respectively, had adverse events leading to discontinuation of investigational product. Only motesanib-treated subjects had hypertension events (5%) that led to discontinuation. Serious adverse events leading to discontinuation of investigational product were reported in 11%, 4%, and 4% of subjects treated with motesanib, placebo, and bevacizumab, respectively (paclitaxel was also discontinued in 60%, 75% and 100% of the motesanib, placebo, and bevacizumab subjects who discontinued investigational product due to SAEs).

Treatment-emergent EOIs of diarrhea and hypertension occurred more frequently in subjects receiving motesanib compared with subjects receiving placebo or bevacizumab. Diarrhea events were reported for 71% of subjects treated with motesanib, 37% of subjects treated with placebo, and 46% of subjects treated with bevacizumab. Hypertension events were reported for 63% of subjects treated with motesanib, 15% of subjects treated with placebo, and 41% of subjects treated with bevacizumab. Gallbladder related disorders were reported more frequently in motesanib-treated subjects (12%) compared to placebo-treated subjects (2%) and bevacizumab-treated subjects (1%), and consisted of cholecystitis and various other gallbladder related disorders. No events of gallbladder perforation were reported.

In order to evaluate left ventricular dysfunction, measurements of LVEF by echocardiogram or MUGA scan were performed at baseline, during therapy, and at the end of study treatment visit in the motesanib, placebo, and bevacizumab treated subjects. While receiving therapy, an absolute decrease from baseline LVEF of ≥ 10% was observed in 31.5%, 18.0% and 15.6% of subjects, respectively. The percentage of subjects with a ≥ 10% absolute decrease in LVEF observed in 2 consecutive timepoints was 9.8% in motesanib-treated subjects compared with 2.2% in the placebo-treated subjects and 5.2% in bevacizumab-treated subjects. The incidence of a maximum relative decrease while on therapy of > 15% in LVEF was higher in subjects receiving motesanib than in those receiving placebo or bevacizumab (30.4%, 11.2% and 10.4%, respectively). The incidence of subjects demonstrating LVEF values below the lower limit of normal was also higher in the subjects receiving motesanib (15.2%, 2.2% and 5.2%, respectively). Of the 28 subjects on motesanib who demonstrated maximum relative decreases in LVEF of > 15%, the majority were able to tolerate continued dosing of motesanib. Post-study measurements were obtained in 14 of these subjects, and the majority had return to baseline or LVEF values ≥ 51% at the time of post-study evaluation.

Adverse events known to be associated with paclitaxel administration were also reviewed. The subject incidence of grade 3 and 4 neutropenia laboratory abnormalities, as well as the subject incidence of adverse events of nausea and vomiting, was higher in the motesanib arm compared to placebo. Other adverse events consistent with paclitaxel administration were similar between the 2 arms.

In general, changes in laboratory values were consistent with results observed in previous motesanib studies (motesanib diphosphate Investigator's Brochure). However, a higher incidence of grade 3 or 4 neutrophil laboratory toxicity (decreased neutrophils), was observed in subjects treated with motesanib (31.5% and 15.2%, respectively) compared with subjects treated with placebo (18% and 5.6%, respectively) or bevacizumab (27.1% and 9.4%, respectively).

The changes observed in systolic and diastolic blood pressure were consistent with the more frequent reports of hypertension in subjects treated with motesanib when compared to subjects treated with placebo or bevacizumab.

Conclusions:

This study did not meet the primary objective of demonstrating higher objective response rate by motesanib as compared to placebo in patients with HER2 negative metastatic breast cancer. However, increases in both the objective response rate and clinical benefit rate were observed in the motesanib arm compared to the placebo arm. These increases were similar to those observed in the bevacizumab arm. The increase in clinical benefit rate in the motesanib arm was significant at the nominal 5% level compared to the placebo. The improvement of motesanib on median PFS is small over placebo, and numerically less than that of bevacizumab. Safety findings in this study are consistent with the emerging safety profile of the product and with that of other products which inhibit the VEGF pathway, including an increased incidence of hypertension and diarrhea in the motesanib-treated subjects compared to placebo or bevacizumab-treated subjects. In addition, the incidence of gallbladder related disorders was higher in the motesanib-treated subjects compared to placebo or bevacizumab-treated subjects; this finding is also consistent with the emerging safety profile of motesanib.

Weekly paclitaxel infusions of 90 mg/m^2 do not markedly impact motesanib exposure upon co-administration in subjects with HER2 negative locally recurrent or metastatic breast cancer; however, co-administration of motesanib and weekly paclitaxel results in a modest increase in the exposure to paclitaxel.

SYNOPSIS

Name of Sponsor: Amgen, Inc.

Name of Finished Product: motesanib diphosphate (also known as motesanib or AMG 706)

Name of Active Ingredient: motesanib diphosphate

Title of Study: A Randomized Phase 2 Trial of Double-blind, Placebo-controlled AMG 706 in Combination With Paclitaxel, or Open-label Bevacizumab in Combination With Paclitaxel as First-line Therapy in Women With HER2 Negative Locally Recurrent or Metastatic Breast Cancer

Investigators and Study Centers: This study was conducted at 71 centers in 12 countries. Centers and principal investigators are listed in Appendix 2.

Publications: Martin M, Roche H, Pinter T, et al. Motesanib, or open-label bevacizumab, in combination with paclitaxel, as first line treatment for HER2-negative locally recurrent or metastatic breast cancer: a phase 2, randomized, double-blind, placebo-controlled study. Lancet Oncol. 2011;12:369-376.

Martin M, Hurvitz S, Kennedy J, et al. CIRG/TORI 010: First analysis of a randomized phase II trial of motesanib plus weekly paclitaxel (P) as first line therapy in HER2-negative metastatic breast cancer (MBC). Eur J Cancer. 2009;7(2 Suppl):259. Abstract O-5001.

Mackey J, Hurvitz S, Crown J, et al. CIRG/TORI 010: 10-month analysis of a randomized phase II trial of motesanib plus weekly paclitaxel as first line therapy in HER2-negative metastatic breast cancer (MBC). Cancer Res. 2009;69(24 Suppl):497S-498S.

Study Period: 01 July 2006 to 31 May 2012

Development Phase: Phase 2

Introduction and Objectives:

This was a phase 2, multicenter, 3-arm, randomized study designed to determine the efficacy of motesanib in combination with paclitaxel in a double-blind, placebo-controlled comparison with paclitaxel alone. This study had 3 treatment arms: paclitaxel plus blinded motesanib placebo (Arm A), paclitaxel plus blinded motesanib (Arm B), paclitaxel plus open-label bevacizumab (Arm C), and an optional rollover to motesanib monotherapy (see protocol in Appendix 1). The primary objective was to determine if treatment with motesanib plus paclitaxel was superior to placebo plus paclitaxel in subjects with HER2 negative locally recurrent or metastatic breast cancer based on objective response rates (ORR). The secondary objectives were to estimate the differences in progression-free survival (PFS), clinical benefit, overall survival time (OS), and duration of response (DOR) between placebo plus paclitaxel (Arm A) and motesanib plus paclitaxel (Arm B). Additional secondary objectives were to estimate the difference in ORR, PFS time, clinical benefit, OS, and DOR between motesanib plus paclitaxel (Arm B) and bevacizumab plus paclitaxel (Arm C) and to evaluate the safety and tolerability in the 3 treatment arms. Details for exploratory endpoints are provided in the protocol (Appendix 1).

Results for the primary analysis were based on data collected from 01 December 2006 (date the first subject was enrolled) to 10 November 2008 (primary analysis data cutoff date, ie, when subjects had been on the study for at least 16 weeks). The Primary Analysis Report also detailed results from the 10-month data analysis using data collected from 01 December 2006 to 08 May 2009 (data cutoff date, ie, when subjects had been on the study for at least 10 months).

At the time of the data cutoff for the primary analysis (10 November 2008), 176 subjects were still on treatment or in study follow-up. This synopsis CSR reports the results of final efficacy, long-term follow-up, and safety data, including any data updates, through the study completion date (31 May 2012). There were no additional pharmacokinetic or biomarker results at the time of the final analysis, and the results for these data, and for the exploratory analyses, can be found in the Primary Analysis Report. All subjects had completed treatment at the time of the final data analysis.

Methodology: Eligible subjects with measurable locally recurrent or metastatic breast cancer were randomly assigned (1:1:1) to receive paclitaxel plus blinded motesanib placebo (Arm A), paclitaxel plus blinded motesanib (Arm B), or paclitaxel plus open-label bevacizumab (Arm C) (see protocol in Appendix 1). Subjects randomized to Arm A, who had documented disease progression as defined in the protocol, were eligible to rollover to treatment with open-label motesanib monotherapy following disease progression. For subjects with disease progression, unblinding of treatment assignment was only performed if the subject wanted to continue treatment following disease progression. After treatment completion, subject status was followed for survival until death or for approximately 42 months from the date that the last subject was randomized, whichever happened first.

Number of Subjects Planned: 273

Number of Subjects Enrolled: 282

Diagnosis and Main Criteria for Eligibility: Subjects were women 18 years of age or older, with Eastern Cooperative Oncology (ECOG) Performance Status of 0 or 1, adequate organ and hematologic function, histologically or cytologically confirmed adenocarcinoma of the breast with measurable (as per modified Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.0) or locally recurrent disease not amenable to resection with curative intent or metastatic disease. Tumors (primary or metastatic) were HER2 negative by fluorescence in-situ hybridization (FISH) or chromogenic in-situ hybridization (CISH), or 0, 1+ overexpression by immunohistochemistry.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Motesanib was administered orally (PO) once daily (QD) at a dose of 125 mg (5 x 25 mg tablets). Placebo equivalent of 125 mg motesanib was administered PO QD.

Manufacturing lot numbers for motesanib were [redacted]

Manufacturing lot numbers for placebo were [redacted]

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
Bevacizumab: 10 mg/kg IV infusion on day 1 of weeks 1 and 3 for each 4-week cycle [Arm C].
Paclitaxel: 90 mg/m^2 IV infusion over 1 hour every week for 3 weeks for each 4-week cycle.

Duration of Treatment: Treatment was continued until disease progression per modified RECIST (Version 1.0), or until unacceptable toxicity or withdrawal of subject consent. Subjects randomized to paclitaxel plus placebo were eligible to receive motesanib monotherapy (125 mg QD) within 2 weeks after disease progression. All subjects were to be followed for survival until death or for up to 42 months from the date that the last subject was randomized, whichever came first.

Study Endpoints:

Efficacy Endpoints:
Primary: Objective tumor response rate (complete response [CR] and partial response [PR]) according to modified RECIST (Version 1.0) as determined by independent centralized radiological review.
Secondary: PFS, duration of response, clinical benefit (incidence of CR, PR and stable disease lasting > 24 weeks), and OS.

Safety Endpoints: Incidence of adverse events and laboratory abnormalities.

[redacted]

Statistical Methods:

Detailed information on the statistical analyses can be found in the Statistical Analysis Plan (see Appendix 7).

Efficacy Analyses: Efficacy analyses were performed on Intent-to-Treat (ITT) Analysis Set (defined per protocol). Subjects were included in the analyses according to their randomized treatment assignment. Analyses were also conducted on the Eligible Analysis Set (ie, all subjects in the ITT analysis set who met all inclusion and exclusion criteria). The primary endpoint of ORR was compared between the Arm A and Arm B groups at the 0.05 level of significance.

Descriptive statistics (number and proportion) for category of best overall tumor response (CR, PR, stable disease, progressive disease [PD], non-evaluable, and missing) were presented for each treatment arm. ORR (PR and CR rates) between the Arm A and Arm B groups were compared using the stratified Cochran-Mantel-Haenszel statistic at the 0.05 level of significance. The 2-sided 95% confidence interval (CI) was calculated for the differences in ORR between Arms A and B.

Estimates of the treatment effect of Arms A and B were obtained for PFS and OS. DOR (responders only) was summarized for each group. For each treatment arm, Kaplan-Meier (KM) curves were presented for each of the time-to-event endpoints. The KM medians (if estimable) were derived, along with their 2-sided 95% confidence intervals. Cox proportional hazards models were used to estimate the hazard ratio for comparing the paclitaxel plus placebo and the paclitaxel plus motesanib groups (adjusted for the stratification factors) and to produce the associated 95% CIs for all time to event endpoints.

Estimates of the difference between the Arm C and Arm B groups for ORR and the time to event variables were provided along with 2-sided 95% CIs. Analyses comparing the ORR and PFS of Arm C and Arm A groups were also conducted. Additionally, the primary and secondary efficacy endpoints were summarized for the subjects in Arm A who received subsequent motesanib monotherapy.

Safety Analyses: Subject incidence rates of treatment-emergent and treatment-related adverse events, prespecified treatment-emergent EOIs, serious adverse events, and adverse events leading to withdrawal were tabulated by treatment groups and by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Adverse event severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Summary statistics (number and percent) for ECHO/MUGA parameters (left ventricular ejection fraction [LVEF]) were provided for prespecified timepoints and percentage change from baseline.

Laboratory parameters were summarized at baseline and end of study (last observed value) including shifts from baseline, maximum and minimum observed post-baseline values, change from baseline to the maximum observed value, minimum observed value, and end of study.

Summary of Results:

Subject Disposition:

The analysis sets for subjects are the same as those in the Primary Analysis Report: 277 subjects were included in the Treated Analysis Set in Arms B, C, and A with 92, 97, and 93 subjects per arm, respectively (Table 14-1.015 and Primary Analysis Report Table 14-1.8 and Table 14-1.15). There were 13 subjects in the Rollover Analysis Set (Table 14-1.015).

The dispositions of the 282 subjects overall by randomized group assignment and for the 13 subjects in the Rollover group are presented in Table 1. Five randomized subjects did not

receive any study treatment. The most common reasons cited for ending study treatment in the 277 subjects who received treatment (for n [%] subjects) were disease progression (158 [57.0%]) and adverse experience (61 [22.0%]) (Table 14-1.009 and Table 14-1.010). Disease progression was reported in 50 (54.3%), 49 (51.0%), and 59 (66%) subjects in Arms B, C, and A, respectively. Adverse experience was reported in 21 (22.8%), 26 (27.1%), and 14 (16%) subjects in Arms B, C, and A, respectively. Disease progression and adverse experience were reported in 85% and 15% of subjects, respectively, in the Rollover treatment group.

Table 1. Disposition of Subjects – Treatment Completion

Disposition	Arm As Randomized			All Randomized Subjects (N = 277)	Rollover Open-label AMG 706 (N = 13)
	Arm B AMG 706 (N = 92)	Arm C Bevacizumab (N = 96)	Arm A Placebo (N = 89)		
Study status					
Completed end of study treatment	92 (100.0%)	96 (100.0%)	89 (100.0%)	277 (100.0%)	13 (100.0%)
End of study treatment reason					
Disease progression	50 (54.3%)	49 (51.0%)	59 (66.3%)	158 (57.0%)	11 (84.6%)
Adverse experience	21 (22.8%)	26 (27.1%)	14 (15.7%)	61 (22.0%)	2 (15.4%)
Other	12 (13.0%)	8 (8.3%)	4 (4.5%)	24 (8.7%)	-
Consent withdrawn from protocol medication	4 (4.3%)	10 (10.4%)	6 (6.7%)	20 (7.2%)	-
Overall consent withdrawn Death	3 (3.3%)	1 (1.0%)	4 (4.5%)	8 (2.9%)	-
Lost to follow-up	2 (2.2%)	2 (2.1%)	1 (1.1%)	5 (1.8%)	-
	0 (0.0%))	0 (0.0%)	1 (1.1%)	1 (0.4%)	-

Note: Data are n (%) subjects. All subjects treated received paclitaxel as per protocol in addition to treatment group listed in table.
Source: Table 14-1.009 and Table 14-1.010

Subject Demographics: The subject demographics at baseline for the ITT and Rollover Analysis Sets are presented in Table 2.

Table 2. Subject Demographics

	Intent-to-Treat Population (N = 282)	Rollover Open-label AMG 706 (N = 13)
Sex	Female = 282 (100%)	Female = 13 (100%)
Age (SD)	54.5 (10.7)	50.0 (12.1)
Race	Caucasian = 246 (87.2%) Asian = 24 (8.5%) Black = 3 (1.1%)	Caucasian = 11 (84.6%) Asian = 2 (15.4%)

SD: standard deviation
Note: Data for sex and race are n (%) subjects. Age is presented as mean (standard deviation).
Source: Table 14-2.001 and Table 14-2.002

Efficacy Results:

Objective Response Rate: ORR, the primary endpoint, was slightly higher for each of the 3 groups (Arms B/C/A: 51%, 51%, and 39%, respectively) (Table 3), in comparison to the primary analysis results (Arms B/C/A: 48%, 45%, and 35%, respectively) (Primary Analysis Report Table 14-4.1.01 and Table 14-4.1.03). In this final analysis, ORR in the Rollover Analysis Set was 8% (Table 14-4.1.03).

ORR as assessed by investigators and those based on best response prior to non-protocol anticancer therapy showed no significant difference in ORR between motesanib-treated subjects and those treated with placebo or bevacizumab in either of these analyses (Table 14-4.1.04 and Table 14-4.1.05, respectively).

Table 3. Objective Response Rate - Intent to Treat and Rollover Analysis Sets

	Arm as Randomized			Rollover
	Arm B AMG 706 (N = 91)	**Arm C Bevacizumab (N = 97)**	**Arm A Placebo (N = 94)**	**Open-label AMG 706 (N = 13)**
Best overall tumor response (n [%])				
Complete response	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Partial response	46 (51%)	49 (51%)	36 (38%)	1 (8%)
Stable disease	33 (36%)	35 (36%)	34 (36%)	4 (31%)
Progressive disease	6 (7%)	8 (8%)	15 (16%)	6 (46%)
Unknown	2 (2%)	4 (4%)	1 (1%)	1 (8%)
Missing	4 (4%)	1 (1%)	7 (7%)	1 (8%)
Objective response rate[a] (%) and exact 95% CI	50.55 [39.86, 61.20]	50.52 [40.17, 60.83]	39.36 [29.44, 49.98]	7.69 [0.19, 36.03]
Comparison versus AMG 706				
Difference in objective response rate and 95% Confidence Interval		-0.03 [-14.33, 14.27]	-11.19 [-25.44, 3.06]	
Stratified Cochran-Mantel-Haenszel test[b]				
Statistic		0.00	2.06	
Degree of Freedom		1	1	
p-value		0.96	0.15	

[a] Objective response rate = the percentage of patients who achieved complete or partial response
[b] Adjusted for the stratification factors
Source: Table 14-4.1.01 and Table 14-4.1.03

Progression-Free Survival: At the time of this final analysis, PFS events (disease progression or died) were reported in over 80% of subjects in each treatment arm (86%, 85%, and 81% for Arms B, C, A, respectively) including within the Rollover analysis group (85%) (Table 14-4.2.01). This is in comparison to approximately 60%, 56%, 55%, and 62% of subjects in Arms B, C, A, and Rollover group at the time of the primary analysis (Primary Analysis Report Table 14-4.2.01).

The median PFS (in months) was also longer in motesanib, bevacizumab, and placebo subjects at final analysis in comparison with primary analysis (Arm B: 11 vs 9.5 months, respectively; Arm C: 15 vs 11 months; Arm A: 11 vs 9 months, respectively) (Table 14-4.2.02 and Table 14-4.2.04; Primary Analysis Report Table 14-4.2.02). For the final analysis, the adjusted hazard ratio for PFS of motesanib versus placebo was 1.08 (95% CI [0.77, 1.52]) and for motesanib versus bevacizumab was 1.35 (95% CI [0.96, 1.90]) (Table 14-4.2.08).

Clinical Benefit Rates: Clinical benefit rates (defined as the percentage of patients who achieved CR, PR or stable disease lasting from randomization > 24 weeks) for Arms B, C, and A in the final analysis (66%, 68%, 48%, respectively; Table 14-4.4.01) were similar to those seen in the primary analysis report (66%, 68%, 49%, respectively; Primary Analysis Report Table 14-4.4.01). In the final analysis, the clinical benefit rate for the Arm B was significantly greater than that of Arm A ($p = 0.016$) and similar in comparison to Arm C ($p = 0.69$).

Overall Survival: The majority of subjects across the 3 treatment groups (75%, 70%, and 68% in Arms B, C, and A, respectively) had died by the time of the final analysis compared with approximately one-third (30%, 28%, and 29%, respectively) of subjects at the time of the primary analysis (Table 14-4.2.01 and Primary Analysis Report Table 14-4.2.01).

Median OS was 25.4, 30.3, and 25.9 months in Arms B, C, and A, respectively, at the time of the final analysis and 25.4 and 22.7 months for Arms B and C, respectively, at the time of the primary analysis (Table 14-4.5.01 and Primary Analysis Report Table 14-4.5.01). Median OS was the same for Arm B in both the final and primary analyses, but was longer in Arm C in the final vs primary analysis.

The adjusted hazard ratio for OS of motesanib versus placebo was 1.02 (95% CI [0.72, 1.45]) in the final analysis vs 0.97 (95% CI [0.55, 1.69]) in the primary analysis (Table 14-4.5.05 and Primary Analysis Report Table 14-4.5.05, respectively). The adjusted hazard ratio for OS of motesanib versus bevacizumab was 1.22 (95% CI [0.86, 1.73]) in the final analysis vs 1.11 (95% CI [0.64, 1.92]) in the primary analysis (Table 14-4.5.05 and Primary Analysis Report Table 14-4.5.05, respectively).

Duration of Response: DOR for subjects who responded was similar to the pattern of results presented in the primary analysis. The shortest median duration of response was with motesanib (9 months in both final and primary analysis), followed by placebo (11 months in final vs 9.5 months in primary analysis), then bevacizumab (16 months in final vs 15 months in primary analysis) (Table 14-4.3.01; Primary Analysis Report Table 14-3.3.01). For the 1 subject in the Rollover Analysis Set who responded, the median duration of response for this subject was 40 months (Table 14-4.3.03).

[redacted]

Patient Reported Outcomes Evaluation: Health State Index and VAS scores were similar to the pattern of results presented in the primary analysis. AUC analyses for the Health State Index or VAS scores did not show any statistically significant differences between treatment groups at Cycle 5 or Cycle 7 (Table 14-8.042, Table 14-8.044, Table 14-8.034, and Table 14-8.036).

[redacted]

Safety Results:

The safety profile of motesanib for the final analysis was generally consistent with that previously reported in the Primary Analysis Report.

In the final analysis, of the 277 subjects in the Safety Analysis Set, 276 (99.6%) of those had at least 1 adverse event (99%, 100%, and 100% in Arms B, C, and A, respectively) (Amgen Table 14-6.1.1) and was the same as that of the primary analysis (Primary Analysis Report Table 14-6.1.1). A summary of incidence of treatment-emergent adverse events is presented in Table 4. Adverse events leading to discontinuation of IP was highest for subjects treated with motesanib (final analysis: 30 [33%] vs primary analysis: 28 [30%] subjects), followed by bevacizumab (final analysis: 26 [27%] vs primary analysis: 22 [23%]), and placebo (final analysis: 11 [12%] vs primary analysis: 12 [13%]) (Amgen Table 14-6.1.1 and Amgen Table 14-6.1.2, and Primary Analysis Report Table 14-6.1.1).

Table 4. Final Analysis: Summary of Subject Incidence of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Arm B AMG 706 (N = 92)	Arm A Placebo (N = 89)	Arm C Bevacizumab (N = 86)	All Subjects (N = 277)	Rollover Open-label AMG 706 (N = 13)
All adverse events[a]	91 (99)	89 (100)	96 (100)	276 (99.6)	13 (100)
Serious adverse events	35 (38)	28 (31)	24 (25)	87 (31)	2 (15)
Treatment-related adverse events / Serious adverse events	82 (89) / 24 (26)	65 (73) / 6 (7)	82 (85) / 7 (7)	229 (83) / 37 (13)	13 (100) / 2 (15)
Grade 3[b]	44 (48) / 16 (17)	10 (11) / 1 (1)	29 (30) / 3 (3)	83 (30) / 20 (7)	3 (23) / 1 (8)
Grade 4[b]	5 (5) / 4 (4)	1 (1) / 1 (1)	0 / 0	6 (2) / 5 (2)	1 (8) / 0
Grade 5[b]	0 / 0	1 (1) / 1 (1)	1 (1) / 1 (1)	2 (1) / 2 (1)	0 / 0
Discontinuation of IP due to adverse event	30 (33)	26 (27)	11 (12)	67 (24)	3 (23)
Discontinuation of IP due to serious adverse event	12 (13)	4 (4)	6 (6)	22 (8)	1 (8)
Fatal treatment-emergent adverse event	1 (1)	4 (4)	2 (2)	7 (3)	1 (8)

Note: Data is n (%) subjects.
[a] AE occurring or worsening on or after 1st dose of study treatment but prior to 30 days after last dose of study treatment
[b] Data are n (%) subjects with treatment-related adverse events / serious adverse events for grade
IP: Investigational Product.
Source: Amgen Table 14-6.1.1 and Amgen Table 14-6.2.1

Table 5. Primary Analysis: Summary of Subject Incidence of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Arm B AMG 706 (N = 92)	Arm A Placebo (N = 89)	Arm C Bevacizumab (N = 86)	All Subjects (N = 277)	Rollover Open-label AMG 706 (N = 13)
All adverse events[a]	91 (99)	89 (100)	96 (100)	276 (99.6)	13 (100)
Serious adverse events	34 (37)	26 (29)	22 (23)	82 (30)	2 (15)
Treatment-related adverse events / Serious adverse events	82 (89) / 22 (24)	64 (72) / 5 (6)	80 (83)/6 (6)	226 (82) / 33 (12)	13 (100) / 2 (15)
Grade 3	44 (48) / 15 (16)	9 (10) / 1 (1)	25 (26) / 2 (2)	78 (28) / 18 (6)	2 (15) / 0
Grade 4	4 (4) / 3 (3)	1 (1) / 1 (1)	0 / 0	5 (2) / 4 (1)	1 (8) / 0
Grade 5	0 / 0	1 (1) / 1 (1)	1 (1) / 1 (1)	2 (1) / 2 (1)	1 (8) / 1 (8)
Discontinuation of IP due to serious adverse event	10 (11)	4 (4)	4 (4)	18 (6)	1 (8)
Fatal Treatment-emergent Adverse event	1 (1)	3 (3)	1 (1)	5 (2)	1 (8)

Note: Data is n (%) subjects.
[a] AE occurring or worsening on or after 1st dose of study treatment but prior to 30 days after last dose of study treatment
IP: Investigational Product.
Source: Primary Analysis Report Table 14-6.1.1 and Table 14-6.1.2

In the final analysis, the most frequently reported treatment-emergent adverse events in subjects (those in which ≥ 20% of subjects overall had at least 1 adverse event listed by number and percent of subjects with adverse event) in the Safety Analysis Set by System Organ Class (SOC) in Arms B, C, and A and Rollover group (by n [%] subjects in Arm B) are present in Table 6. Gastrointestinal disorders were the most frequently reported adverse events overall (238 [86%]), in Arm B (84 [91%]), and in the Rollover group (9 [69%]) (Amgen Table 14-6.7.1 and Amgen Table 14-6.8.1).

Table 6. Treatment-emergent Adverse Events by System Organ Class Occurring in ≥ 20% of Subjects in Motesanib Arm (Safety Analysis Set)

System Organ Class	Arm B AMG 706 (N = 92)	Arm C Bevacizumab (N = 96)	Arm A Placebo (N = 89)	Open-label AMG 706 (N = 13)
Gastrointestinal Disorders	84 (91.3%)	80 (83.3%)	74 (83.1%)	9 (69.2%)
Nervous System Disorders	80 (87.0%)	71 (74.0%)	68 (76.4%)	8 (61.5%)
Skin and Subcutaneous Tissue Disorders	77 (83.7%)	84 (87.5%)	71 (79.8%)	4 (30.8%)
General Disorders and Administration Site Conditions	78 (84.8%)	82 (85.4%)	71 (79.8%)	8 (61.5%)
Vascular Disorders	65 (70.7%)	52 (54.2%)	40 (44.9%)	8 (61.5%)
Respiratory, Thoracic and Mediastinal Disorders	60 (65.2%)	72 (75.0%)	49 (55.1%)	5 (38.5%)
Musculoskeletal and Connective Tissue Disorders	58 (63.0%)	70 (72.9%)	57 (64.0%)	7 (53.8%)
Infections and Infestations	54 (58.7%)	73 (76.0%)	37 (41.6%)	2 (15.4%)
Metabolism and Nutrition Disorders	43 (46.7%)	36 (37.5%)	24 (27.0%)	3 (23.1%)
Investigations	42 (45.7%)	34 (35.4%)	24 (27.0%)	4 (30.8%)
Psychiatric Disorders	31 (33.7%)	39 (40.6%)	25 (28.1%)	1 (7.7%)
Eye Disorders	26 (28.3%)	26 (27.1%)	14 (15.7%)	1 (7.7%)
Cardiac Disorders	20 (21.7%)	13 (13.5%)	11 (12.4%)	0 (0%)

Source: Table 14-6.007 and Table 14-6.008

Adverse events reported more frequently (≥ 5%) in Arm B vs either Arm C or A were gastrointestinal disorders (91% vs 83% and 83%, respectively), nervous system disorders (87% vs 74% and 76%, respectively), and vascular disorders (71% vs 54% and 45%, respectively) (Table 14-6.007). The most frequently reported adverse events (≥ 20% of subjects overall in the Safety Analysis Set by n [%] subjects) are presented in Table 7. Adverse events that were reported more frequently (≥ 5%) in Arm B vs either Arm C or A included diarrhea (71% vs 49% and 38%), hypertension (63% vs 41% and 16%), nausea (60% vs 50% and 41%), abdominal pain (46% vs 17% and 22%), and vomiting (41% vs 25% and 26%) (Table 14-6.11.1.1). Adverse events reported more frequently (≥ 5%) in Arm C vs either Arm B or A included alopecia (74% vs 62% and 66%), peripheral sensory neuropathy (56% vs 49% and 42%), epistaxis (45% vs 35% and 19%), nail disorder (35% vs 27% and 22%), and cough (38% vs 23% and 24%) (Table 14-6.11.1.1).

Table 7. Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥ 20% of Subjects in Motesanib Arm (Safety Analysis Set)

Preferred Term	Arm B AMG 706 (N = 92)	Arm C Bevacizumab (N = 96)	Arm A Placebo (N = 89)	All Subjects (N = 277)	Open-label AMG 706 (N = 13)
Number of subjects reporting adverse events	91 (99)	96 (100)	89 (100)	276 (100)	13 (100)
Diarrhoea	65 (71)	47 (49)	34 (38)	146 (53)	7 (54)
Hypertension	58 (63)	39 (41)	14 (16)	111 (40)	8 (62)
Alopecia	57 (62)	71 (74)	59 (66)	187 (68)	1 (8)
Fatigue	56 (61)	46 (48)	55 (62)	157 (57)	6 (46)
Nausea	55 (60)	48 (50)	41 (46)	144 (52)	6 (46)
Peripheral sensory neuropathy	45 (49)	54 (56)	37 (42)	136 (49)	1 (8)
Abdominal pain	42 (46)	16 (17)	20 (22)	78 (28)	1 (8)
Vomiting	38 (41)	24 (25)	23 (26)	85 (31)	2 (15)
Decreased appetite	37 (40)	28 (29)	15 (17)	80 (29)	3 (23)
Constipation	35 (38)	33 (34)	28 (31)	96 (35)	2 (15)
Headache	33 (36)	29 (30)	26 (29)	88 (32)	5 (38)
Epistaxis	32 (35)	43 (45)	17 (19)	92 (33)	2 (15)
Dyspnoea	27 (29)	22 (23)	17 (19)	66 (24)	1 (8)
Weight decreased	27 (29)	19 (20)	9 (10)	55 (20)	3 (23)
Dysgeusia	26 (28)	26 (27)	12 (13)	64 (23)	2 (15)
Rash	26 (28)	28 (29)	18 (20)	72 (26)	0 (0)
Nail disorder	25 (27)	34 (35)	20 (22)	79 (29)	1 (8)
Asthenia	23 (25)	25 (26)	16 (18)	64 (23)	1 (8)
Cough	21 (23)	36 (38)	21 (24)	78 (28)	2 (15)
Pain in extremity	20 (22)	23 (24)	19 (21)	62 (22)	1 (8)
Arthralgia	19 (21)	18 (19)	14 (16)	51 (18)	1 (8)
Bone pain	19 (21)	20 (21)	17 (19)	56 (20)	1 (8)
Dyspepsia	19 (21)	17 (18)	16 (18)	52 (19)	2 (15)
Myalgia	19 (21)	17 (18)	17 (19)	53 (19)	2 (15)
Back pain	17 (18)	25 (26)	14 (16)	56 (20)	1 (8)
Stomatitis	16 (17)	31 (32)	10 (11)	57 (21)	1 (8)

Note: Data are n (%) subjects.
Source: Table 14-6.11.1.1

In the final analysis, the most frequently reported serious adverse events (occurring in ≥ 1% of subjects overall) were abdominal pain (6 [2%]), diarrhea (5 [2%]), vomiting (5 [2%]), fatigue (5 [2%]), pyrexia (5 [2%]), cellulitis (5 [2%]), dyspnea (5 [2%]), neutropenia (5 [2%]), asthenia (4 [1%]), pulmonary embolism (4 [1%]), nausea (3 [1%]), anemia (3 [1%]), febrile neutropenia (3 [1%]), cholecystitis (3 [1%]), transient ischemic attack (3 [1%]), tachycardia (3 [1%]), femur fracture (3 [1%]), and back pain (3 [1%]) (Table 14-6.023). In the primary analysis, the most frequently reported serious adverse events (occurring in ≥ 1% of subjects overall) were diarrhea (4 [1%] subjects), cholecystitis (3 [1%]), fatigue (3 [1%]), abdominal pain (3 [1%]), asthenia (2 [1%]), hypertension (2 [1%]), nausea (2 [1%]), stomatitis (2 [1%]), transient ischemic attack (3 [1%]), and vomiting (2 [1%]) (Primary Analysis Report Table 14-6.11.6.1).

The scope of adverse events terms used to define the events of interest of diarrhea, hypertension, reversible posterior leukoencephalopathy syndrome events, cholecystitis and gallbladder perforation, thromboembolic events, left ventricular dysfunction, hypothyroidism, hemorrhagic events, gastrointestinal perforation, fistula and intra-abdominal abscess events, proteinuria and nephrotic syndrome, impaired wound healing, pancreatitis, hepatic toxicity, hematologic events, and peripheral neuropathy is presented in Appendix 8. In the Safety Analysis Set, 259 (94%) subjects had at least 1 prespecified adverse event of interest, with grade 1 events occurring in 43 (16%) subjects, grade 2 in 86 (31%) subjects, grade 3 in 107 (39%) subjects, grade 4 in 18 (6%) subjects, and grade 5 in 5 (2%) subjects (Table 8). Grade 3 adverse events of interest were reported most frequently in Arm B vs either Arm C or A (52% vs 42% and 21%, respectively). Grade 4 events were reported in 7 (8%), 6 (6%), and 5 (6%) of subjects in Arms B, C, and A, respectively. Grade 5 events were reported in 1 subject in each of Arms B and C (coma and cardiopulmonary failure, respectively) and 3 subjects in Arm A (1 of hyperbilirubinemia and 2 of hepatic failure).

The most frequently adverse events of interest reported in Arm B were in the acute pancreatitis category (71 [77%] subjects); in the Rollover group, the events of interest were most frequently reported in the hypertension category (8 [62%]).

Table 8. Treatment-Emergent Adverse Events of Interest by Category Occurring in ≥ 10% of Subjects in the Motesanib Arm (Safety Analysis Set)

Adverse Event Category	Arm B AMG 706 (N = 92)	Arm A Placebo (N = 89)	Arm C Bevacizumab (N = 96)	All Subjects (N = 277)	Open-label AMG 706 (N = 13)
Subjects with any adverse event of interest	89 (97)	82 (92)	88 (92)	259 (94)	
Worst grade of 1	8 (9)	23 (26)	12 (13)	43 (16)	3 (23)
Worst grade of 2	25 (27)	32 (36)	29 (30)	86 (31)	7 (54)
Worst grade of 3	48 (52)	19 (21)	40 (42)	107 (39)	2 (15)
Worst grade of 4	7 (8)	5 (6)	6 (6)	18 (6)	0 (0)
Worst grade of 5	1 (1)	3 (3)	1 (1)	5 (2)	1 (8)
Acute pancreatitis	71 (77)	56 (63)	60 (63)	187 (68)	7 (54)
Peripheral neuropathy	67 (73)	58 (65)	66 (69)	191 (69)	2 (15)
Non-infectious diarrhea	65 (71)	34 (38)	49 (51)	148 (53)	7 (54)
Hypertension	58 (63)	14 (16)	39 (41)	111 (40)	8 (62)
Haemorrhage terms (excl laboratory terms)	42 (46)	24 (27)	54 (56)	120 (43)	2 (15)
Cardiomyopathy	35 (38)	26 (29)	30 (31)	91 (33)	3 (23)
Cardiac failure	25 (27)	27 (30)	27 (28)	79 (29)	1 (8)
Reversible posterior Leukoencephalopathy syndrome	13 (14)	12 (13)	8 (8)	33 (12)	1 (8)
Gallbladder related disorders	11 (12)	2 (2)	1 (1)	14 (5)	0 (0)
Drug related hepatic disorders - comprehensive search	9 (10)	8 (9)	4 (4)	21 (8)	1 (8)

Note: Date are n (%)
Source: Amgen Table 14-6.6.1 and Amgen Table 14-6.6.2

Adverse events of interest that were reported more frequently (≥ 5%) in Arm B vs either Arm C or A included (by MedDRA preferred term) diarrhea, hypertension, nausea, abdominal pain, vomiting, dyspnea, chest pain, peripheral neuropathy, abdominal distension, left ventricular dysfunction, paraesthesia, and blurred vision (Table 9). Adverse events more frequently reported (≥ 5%) in Arm C vs either Arm B or A included peripheral sensory neuropathy, epistaxis, upper abdominal pain, and proteinuria. Adverse events more frequently reported (≥ 5%) in Arm A vs either Arm B or C included oedema peripheral, muscular weakness, and memory impairment (Amgen Table 14-6.6.1).

Table 9. Treatment-Emergent Adverse Events of Interest by Preferred Term Occurring in ≥ 5% of Subjects in the Motesanib Arm vs Bevacizumab or Placebo Arms (Safety Analysis Set)

Preferred Term	Arm B AMG 706 (N = 92)	Arm C Bevacizumab (N = 96)	Arm A Placebo (N = 89)	All Subjects (N = 277)
Diarrhoea	65 (71)	47 (49)	34 (38)	146 (53)
Hypertension	58 (63)	39 (41)	14 (16)	111 (40)
Nausea	55 (60)	48 (50)	41 (46)	144 (52)
Abdominal pain	42 (46)	16 (17)	20 (22)	78 (28)
Vomiting	38 (41)	24 (25)	23 (26)	85 (31)
Dyspnoea	27 (29)	22 (23)	17 (19)	66 (24)
Chest pain	10 (11)	6 (6)	6 (7)	22 (8)
Neuropathy peripheral	10 (11)	4 (4)	11 (12)	25 (9)
Abdominal distension	7 (8)	1 (1)	2 (2)	10 (4)
Left ventricular dysfunction	8 (9)	3 (3)	1 (1)	12 (4)
Paraesthesia	8 (9)	8 (8)	3 (3)	19 (7)
Vision blurred	6 (7)	7 (7)	2 (2)	15 (5)

Note: Date are n (%)
Source: Amgen Table 14-6.6.1 and Amgen Table 14-6.6.2

Adverse events of interest that were considered serious occurred in 52 (19%) subjects overall (Table 14-6.8.1); 25 (27%), 11 (11%), and 16 (18%) in Arms B, C, and A, respectively. Three subjects had grade 4 adverse events of interest that were considered related to motesanib (preferred terms: gamma-glutamyltransferase increased, hepatic encephalopathy, and pancytopenia), and no subjects had grade 5 adverse events of interest that were considered by the investigator to be related to motesanib (Table 14-6.7.1).

At the time of the final analysis, a QTcF interval > 500 msec was reported in 3 (3%), 3 (3%), and 2 (2%) in Arms B, C, and A, respectively, and a QTcF increase from baseline > 60 msec was reported in 10 (11%), 8 (8%), and 6 (7%) in Arms B, C, and A, respectively (Table 14-8.015). In contrast, at the time of the primary analysis, 3 subjects experienced a QTcF interval > 500 msec and 9 subjects experienced a QTcF increase from baseline > 60 msec (Primary Analysis Report Table 14-8.15).

Seven subjects in the Safety Analysis Set and 1 subject in the Rollover Analysis Set experienced fatal adverse events (ie, died during study or from adverse events that began within 30 days of the last protocol-specified treatment administration) (Table 10).

Table 10. Subject Incidence of Fatal Adverse Events by System Organ Class and Preferred Term (Safety and Rollover Period Analysis Sets)

System Organ Class Preferred Term	Arm B AMG 706 (N = 92)	Arm A Placebo (N = 89)	Arm C Bevacizumab (N = 96)	All Subjects (N = 277)	Rollover (N = 13)
Subjects with any fatal adverse event	1 (1)	4 (4)	2 (2)	7 (3)	1 (8)
Cardiac disorders	0 (0)	0 (0)	1 (1)	1 (0)	0 (0)
Cardiopulmonary failure	0 (0)	0 (0)	1 (1)	1 (0)	0 (0)
Hepatobiliary disorders	0 (0)	3 (3)	0 (0)	3 (1)	1 (8)
Hepatic failure	0 (0)	2 (2)	0 (0)	2 (1)	1 (8)
Hyperbilirubinaemia	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)
Infections and infestations	0 (0)	0 (0)	1 (1)	1 (0)	0 (0)
Lower respiratory tract infection	0 (0)	0 (0)	1 (1)	1 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1 (1)	0 (0)	1 (0)	0 (0) 0 (0)
Lymphangiosis carcinomatosa	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)
Nervous system disorders	1 (1)	0 (0)	0 (0)	1 (0)	0 (0)
Coma	1 (1)	0 (0)	0 (0)	1 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)
Diffuse alveolar damage	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)
Respiratory failure	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)

Note: Data are n (%) subjects
Grade is based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated December 12, 2003.
The Safety Analysis Set includes all subjects who are randomized and received at least one dose of assigned Motesanib, Placebo or Bevacizumab. Subjects are included in the treatment group for which they received therapy.
Treatment-emergent adverse events includes adverse events that began between the first administration of randomized protocol-specified treatment and 30 days after the last administration of the randomized protocol-specified treatment. Adverse events happening during the roll over period are excluded.
Subjects may be represented in multiple System Organ Classes and in multiple preferred terms within a System Organ Class.
Preferred terms are assigned based on MedDRA version 15.0.
Source: *Amgen Table 14-6.12.1 and Amgen Table 14-6.12.2*

For 2 of the subjects, deaths were considered related to IP; 1 subject who received bevacizumab experienced a fatal event of cardiopulmonary failure that was attributed to paclitaxel or bevacizumab and 1 subject who received placebo only experienced a fatal event of hepatic failure that was attributed to motesanib; however, this placebo subject never received any doses of motesanib and the identity of IP was still blinded at time cause of death was indicated on subject case report form as toxicity related to motesanib (Listing 10.05 and Listing 10.06). One subject in the Rollover Analysis Set experienced a fatal adverse event of hepatic failure that was not considered related to IP.

In the final analysis, of the 92 subjects in the Safety Analysis Set who received ≥ 1 dose of motesanib, the majority of these subjects (50 [54%]) did not have adjustments to their motesanib dose. Most dose adjustments in subjects (37 [40%]) occurred at the 125 to 100 mg dose level (Table 14-3.5).

Protocol deviations included missed doses or administration error of IP, electrocardiogram (ECG) not assessed within 14 days of study randomization, use of concomitant medications, LVEF and ECG assessments outside visit window, and missing laboratory values. One subject (Subject 10255) who did not meet eligibility criteria (had brain metastasis at baseline) was enrolled and randomized to Arm C (ie, Bevacizumab) (DCF 70230).

Conclusions: Key conclusions of the primary analysis report were: 1) the study did not meet the primary objective of demonstrating a higher objective response rate for motesanib/paclitaxel as compared to placebo/paclitaxel in subjects with HER2 negative metastatic breast cancer, 2) similar increases in both the objective response rate and clinical benefit rate were observed in the motesanib and bevacizumab arms compared to the placebo arm, 3) safety findings were consistent with the emerging safety profile of motesanib and with that of other products that inhibit the VEGF pathway, and 4) weekly paclitaxel infusions of 90 mg/m^2 did not markedly impact motesanib exposure upon co-administration in subjects with HER2 negative locally recurrent or metastatic breast cancer; however, co-administration of motesanib and weekly paclitaxel resulted in a modest increase in the exposure to paclitaxel.

This Final Analysis Report updates the previous Primary Analysis Report with additional efficacy and safety data collected through study completion.

For the efficacy endpoints, overall the efficacy results were generally consistent with those in the primary analysis. At the time of this final analysis, ORR was slightly higher for each of the 3 groups in comparison to the primary analysis results and higher in the motesanib and bevacizumab arms vs placebo. The median PFS (in months) was also longer in motesanib, bevacizumab, and placebo subjects at final analysis in comparison with primary analysis (Arm B: 11 vs 9.5 months, respectively; Arm C: 15 vs 11 months; Arm A: 11 vs 9 months, respectively).For PFS events (disease progression or died), the adjusted hazard ratio for PFS of motesanib versus placebo was 1.08 (95% CI [0.77, 1.52]) and for motesanib versus bevacizumab was 1.35 (95% CI [0.96, 1.90]).

Median OS was 25.4, 30.3, and 25.9 months in Arms B, C, A, respectively, at the time of the final analysis and 25.4 and 22.7 months for Arms B and C, respectively, at the time of the primary analysis. Median OS was the same for Arm B in both the final and primary analyses, but was longer in Arm C in the final vs primary analysis. The OS adjusted hazard ratio for OS of motesanib versus placebo was 1.02 (95% CI [0.72, 1.45]) in the final analysis vs 0.97 (95% CI [0.55, 1.69]) in the primary analysis. In the final analysis, the adjusted hazard ratio for OS of motesanib versus bevacizumab was 1.22 (95% CI [0.86, 1.73]) in the final analysis vs 1.11 (95% CI [0.64, 1.92]) in the primary analysis. Clinical benefit rates in the final analysis were similar to those seen in the Primary Analysis Report, with Arm B being significantly greater than that of Arm A in the final analysis ($p = 0.016$ in the final analysis).

The safety profile of motesanib for the final analysis was generally consistent with that previously reported in the primary analysis report. The Final Analysis results showed no shifts in data that would change the conclusions described in the Primary Analysis Report.