2. SYNOPSIS

Name of Sponsor: Amgen, Inc.

Name of Finished Product: Motesanib (AMG 706)

Name of Active Ingredient: Motesanib diphosphate

Title of Study: An Open Label Treatment Extension Study of AMG 706

Investigator(s) and Study Center(s): This study was conducted at 36 study sites that treated subjects in previous motesanib studies in the United States, Canada, Europe, and Australia (Appendix 2).

Publication(s): None to date

Study Period: 09 Dec 2005 to 26 July 2012 (first subject enrolled to last subject completed follow-up)

Development Phase: 2

Introduction and Objectives:

This was a multicenter, open-label study that permitted subjects who completed the planned duration of treatment on a separate Amgen motesanib study and who met additional study eligibility criteria to continue treatment with motesanib monotherapy. Motesanib was administered at the same dose level and schedule that the subject received at the conclusion of the previous motesanib study. Subjects were evaluated at least every 4 weeks. These study visits included a standard of care clinical assessment with collection of vital signs, adverse events, concomitant medications, and laboratory tests. Subjects were evaluated for tumor response per standard of care at the discretion of the investigator.

The primary objective was to provide ongoing treatment with motesanib monotherapy for those subjects who have completed the planned duration of treatment with motesanib on a separate Amgen protocol and demonstrated continuing clinical benefit from motesanib therapy, or for those who were not eligible to remain on a separate Amgen protocol for reasons other than motesanib intolerance, but continue to, or have the potential to, experience clinical benefit as assessed by the principal investigator. The secondary objective was to evaluate the safety profile of motesanib, including adverse events and serious adverse events, for all subjects on continued motesanib treatment.

Methodology:

Number of Subjects Planned: The sample size was dependent upon the number of subjects that transition into this study from separate Amgen motesanib protocols.

Number of Subjects Enrolled:

Sex: Female: 40 (43%) subjects; Male: 54 (57%) subjects

Age: Mean 57.0 years (standard deviation [SD] = 13.8)

Ethnicity (Race): White or Caucasian: 84 (89%) subjects; Hispanic or Latino: 9 (10%) subjects; Other: 1 (1%) subjects

Tumor Type: Thyroid: 79 (84%); Gastrointestinal stromal tumor (GIST): 7 (7%); Kidney: 2 (2%); Cervix: 1 (1%); Non-small cell lung: 1 (1%); Stomach: 1 (1%); Other: 3 (3%)

Diagnosis and Main Criteria for Eligibility: Females or males, ≥ 18 years old with solid tumors and stable disease or better, who were previously treated in and completed a motesanib Amgen protocol and are no longer eligible to continue motesanib treatment on a separate Amgen protocol for reasons other than motesanib intolerance, but were receiving or had the potential to receive clinical benefit from motesanib in the judgment of the investigator, and had not been off

motesanib treatment for > 42 days before study day 1, and did not have uncontrolled hypertension or laboratory values that would preclude participation.

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

100 mg and 25 mg motesanib tablets taken orally

[redacted]

Duration of Treatment: Until disease progression or loss of clinical benefit

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number:
Not applicable

Study Endpoints

Study endpoint included safety (serious adverse events, adverse events, blood pressure, and laboratory parameters), tumor response, and progression-free survival (PFS).

Statistical Methods: Descriptive statistics were provided for safety data and disease status. Continuous measurements were summarized using mean, standard deviation, median, interquartile range, range, and number of subjects. For discrete data, the frequency and percent distribution were provided. All assessments were assigned to an assessment visit based on visit windows and actual study day of assessment.

Efficacy analyses included summaries of tumor response (frequency, percent), PFS time, and overall survival (OS) time (Kaplan-Meier [K-M] estimates of median time and their 2-sided 95% confidence intervals [CIs]). The 95% CI for the K-M estimate was calculated using the Brookmeyer and Crowley method.

Safety analyses were carried out for all subjects who received ≥ 1 dose of motesanib during the study and included tabular summaries of incidences of adverse events, summary statistics for blood pressure and laboratory parameters for baseline, on-study, and change from baseline measurements.

Summary of Results:

Subject Disposition: A total of 94 subjects were enrolled in this study and were included in the Safety Analysis Set. The median duration of therapy for the 125 mg QD, 100 mg QD, 75 mg QD, 75 mg BID, and 150 mg BID groups was 125, 100, 77, 142, and 291 days, respectively. The most frequently reported reasons (occurring in ≥ 10% of subjects) for ending motesanib treatment was disease progression (45%; 42/94) and adverse event (21%; 20/94). Nine subjects died during the study; 8 of them within 30 days of last dose of motesanib and 1 subject after the 30-day follow-up period.

Efficacy Results: The best tumor response for a majority of subjects (67%) was stable disease followed by progressive disease (PD) in 18% of subjects and partial response in 7% of subjects. The median PFS was approximately 22 months (calculated from Day 1 of the parent Amgen protocol). The median OS was not estimable.

Safety Results: The majority (98%; 92/94) of subjects experienced a treatment-emergent adverse event with 53% of adverse events being grade 3, 4% grade 4, and 10% grade 5. The most frequently reported treatment-emergent adverse events grade ≥ 3 (occurring in ≥ 5% of subjects) were abdominal pain (10%), cholecystitis (6%), diarrhea (6%), and fatigue (6%). A total of 78% of treatment-emergent adverse events were considered treatment related. The most frequently reported treatment-related adverse events grade ≥ 3 (occurring in ≥ 5% of subjects) were abdominal pain (7%), fatigue (6%), and cholecystitis (5%). Serious adverse events were reported in 55% (52/94) of subjects with cholecystitis being the most common (occurring in 7% [7/94] of subjects). Cholecystitis was the only serious adverse event that occurred in > 2 subjects (occurring in 6% [6/94] of subjects). Serious treatment-related adverse events occurred in 23% (22/94) of subjects. Laboratory abnormalities occurred in 99% (93/94) of

subjects. Over half of subjects (56%; 53/94) experienced grade 3 or 4 laboratory toxicity. The most common laboratory toxicity with worst grade of 3 or 4 was a decrease in lymphocytes occurring in 23% (22/94) of subjects. An increase in lipase with worst grade of 3 or 4 occurred in 15% (14/94) of subjects.

Conclusions: The majority (67%) of the 94 subjects in this extension study achieved a best response of stable disease and subjects had a median PFS of 22 months. The median duration of therapy for the 125 mg QD, 100 mg QD, 75 mg QD, 75 mg BID, and 150 mg BID groups was 125, 100, 77, 142, and 291 days, respectively. The most common adverse events reported during this study included diarrhea, fatigue, nausea, and abdominal pain. Nine subjects died during the study with disease progression as the cause of death in 5 of these subjects. The occurrences of adverse events and laboratory abnormalities in this study are consistent with previous studies, and no new safety signals were identified in this study.