2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA

Name of Finished Product: Not applicable

Name of Active Ingredient: AMG 706

Title of Study: An Open Label Study of AMG 706 in Subjects with Advanced Gastrointestinal Stromal Tumors (GISTs) who Developed Progressive Disease or Relapsed While on Imatinib Mesylate

Investigator(s) and Study Center(s): This study was conducted at 29 sites in the United States, Europe, and Canada. See Appendix 4 for a complete list of investigators and study centers.

Publication: Benjamin R, Schoffski P, Hartmann JT, et al. Initial results of a multicenter single-arm phase 2 study of AMG 706, an oral multi-kinase inhibitor, for the treatment of advanced imatinib-resistant gastrointestinal stromal tumors (GIST). Presented at: 12th Annual Meeting of the Connective Tissue Oncology Society; 04 November 2006: Venice, Italy. Available from: http://www.ctos.org/meeting/2006/program06.asp. Accessed 22 July 2007.

Study Period: The long-term follow-up assessments for this study are ongoing. This report includes a study period of 04 October 2004 (date first subject enrolled) to 13 November 2006 (data cutoff).

Development Phase: 2

Introduction and Objectives: GIST is a rare stromal neoplasm that arises from the muscularis mucosa or muscularis propria layers and which represents the most common mesenchymal tumor of the gastrointestinal tract, accounting for 5% of all sarcomas. It has been estimated that approximately 4,500 to 6,000 GIST cases may occur in the United States annually (Demetri et al, 2004). Although surgery is the mainstay of initial therapy for nonmetastatic GIST, approximately half of patients present with metastatic disease (DeMatteo et al, 2000). GISTs are resistant to chemotherapy and radiotherapy. Approximately 14% to 18% of advanced GIST patients will suffer progressive disease despite adequate first-line treatment with imatinib mesylate (initial resistance) (Benjamin et al, 2003; Demetri et al, 2002). Many patients in whom the disease initially responded to imatinib mesylate eventually develop a disease recurrence (late resistance) (Blanke et al, 2004). A medical need exists for second-line therapy for patients with GIST that develop progressive disease while taking imatinib mesylate. Sunitinib malate (Sutent® Prescribing Information, 2007), an oral multikinase inhibitor, has recently been approved for the treatment of patients with advanced renal cell carcinoma and GIST after disease progression on, or intolerance to, imatinib mesylate (Gleevec®).

AMG 706 is a highly selective VEGFr agent administered orally that is being evaluated for its ability to inhibit angiogenesis by targeting vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR1-3). It also inhibits platelet-derived growth factor receptor (PDGFR), and stem cell factor receptor (c-kit), which may also confer direct antitumor activity. Currently, the AMG 706 program is in phase 2 development as monotherapy in thyroid cancer and in combination with other anticancer therapies to treat subjects with non-small cell lung cancer (phase 3), breast cancer, colorectal cancer, and other solid tumors. AMG 706 also has activity against the functional receptor for glial cell line-derived neurotrophic factor (RET) (Coxon et al, 2006).

This phase 2, multicenter, open-label, single-arm study was designed to evaluate the safety, efficacy, and pharmacokinetics (PK) of AMG 706 in subjects with advanced GIST who experienced progressive disease during previous imatinib mesylate therapy. The primary objective of the study was to evaluate the effect of AMG 706 treatment on the objective response

rate as assessed by modified Response Evaluation Criteria in Solid Tumor (RECIST; described in [redacted] charter in Appendix 23) in subjects with advanced GISTs who developed progressive disease or relapsed per modified RECIST while receiving imatinib mesylate.

Methodology: The protocol for this study is provided in Appendix 1. Eligible subjects self-administered a daily oral dose of 125 mg AMG 706 for a maximum treatment period of 48 weeks until evidence of disease progression, unacceptable toxicity, consent withdrawal, or death. Subjects with perceived clinical benefit, in the opinion of the investigators, were allowed to continue AMG 706 treatment in extension Study [redacted].

Tumor evaluation was measured by contrast-enhanced computed tomography (CT) scan (or magnetic resonance imaging) at baseline during screening, after 8 weeks, and every 8 weeks thereafter, and by [^{18}F]-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) at baseline (following imatinib mesylate washout) and after 8 weeks.

Number of Subjects Planned: 100 subjects evaluable for efficacy analyses (prestudy disease progression by modified RECIST and confirmed by the independent eligibility review committee [IERC])

Number of Subjects Enrolled: A total of 155 subjects were screened for this study and 139 subjects were subsequently enrolled (additional subjects enrolled to ensure ≥ 100 subjects would meet criteria of prestudy disease progression confirmed by independent central radiographic review). Of the 139 subjects enrolled, 138 subjects were treated.

Sex: 84 men (61%), 54 women (39%)

Mean (SD) Age: 60.1 (12.0) years, range: 25 to 90 years

Ethnicity (Race): 118 white (86%), 8 Hispanic/Latino (6%), 6 black (4%), 4 Asian (3%), 2 other (1%)

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men and women ≥ 18 years old with histologically-confirmed GIST that expressed c-kit/CD117, documented treatment with and disease progression despite imatinib mesylate ≥ 600 mg daily for ≥ 8 weeks, discontinuation of imatinib mesylate ≥ 7 days before study day 1, presence of ≥ 1 measurable (per modified RECIST) and progressing tumor lesion not previously treated with radiotherapy or embolization that could be evaluated by CT or magnetic resonance imaging, and a Karnofsky performance score ≥ 60.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 706 125 mg daily self-administered orally as one 100-mg tablet and one 25-mg tablet. The manufacturing fill lot numbers for 100 mg tablets were [redacted], and for 25-mg tablets were [redacted]. Lot numbers administered to individual subjects are presented in Appendix 18.

Duration of Treatment: ≤ 48 weeks

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: None

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Study Endpoints

Efficacy Endpoints: The primary efficacy endpoint was confirmed objective response (complete response [CR] or partial response [PR]) as determined by independent central radiographic review and defined using modified RECIST. Secondary efficacy endpoints included duration of response, progression-free survival, time to disease progression, time to response, overall

survival, patient-reported outcomes, performance status, palliative response, use of opioid analgesics (in mg morphine equivalents), objective response by ^{18}FDG-PET at week 8 (Stroobants et al, 2003), and objective response by size changes and/or target tumor density changes in Hounsfield Units (also known as Choi criteria; Choi et al, 2007, Choi et al, 2003) at week 8.

Safety Endpoints: The incidence of adverse events (included all treatment-emergent, treatment-related, serious, and National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0 grades 3 and 4 events).

PK Endpoints: The primary AMG 706 PK endpoints were maximum observed plasma concentration [C_{max}], terminal elimination half-life [$t_{1/2,z}$], area under the plasma concentration-time curve from time 0 to 24 hours after dosing [AUC_{0-24}], and concentration at 24 hours after dosing [C_{24}]). Additional PK parameters included the time C_{max} occurred (t_{max}), area under the plasma concentration versus time curve from 0 to infinity (AUC_{0-inf}) and apparent plasma clearance (CL/F). [redacted]

Statistical Methods: The primary efficacy analysis was performed on the per-protocol analysis set ($\geq$ 1 dose of investigational product and IERC-confirmed prestudy disease progression) after all subjects still receiving AMG 706 had been followed for $\geq$ 24 weeks after study enrollment or had completed safety follow up, whichever came first. The primary endpoint of confirmed objective response rate (CR or PR) by modified RECIST, as determined by independent central radiographic review, was provided with its exact 2-sided 95% confidence intervals.

Adverse events were summarized by body system and preferred term according to the MedDRA preferred term dictionary. Number and percent of subjects who experienced adverse events were tabulated. Summary statistics were provided for all clinical laboratory evaluations, vital signs, changes in electrocardiogram QTc intervals, baseline measurements (demographics; height; weight; Karnofsky performance status; geographical region; resistance to imatinib mesylate; prior chemotherapy, radiotherapy, or other therapy; time from disease diagnosis; time since last disease therapy; CD117 expression; tumor mutation status; and gastrectomy status) and on-study measurements, including end-of-study and changes from baseline. Tables of shifts from baseline for selected laboratory values and vital signs were also provided.

The PK parameters of AMG 706 were estimated using standard noncompartmental PK methods and summarized by dose level using standard summary statistics (means, standard deviations, medians, minimums, maximums, etc.) for intensive and peak/trough assays. Individual plasma/time profiles were summarized by dose level. The PK parameters were evaluated as a function of study day.

Summary of Results:

Subject Disposition: Of 139 enrolled subjects, 138 subjects self-administered $\geq$ 1 dose of AMG 706. One subject was enrolled but did not receive AMG 706. After subject enrollment, prestudy disease progression was confirmed in 120 subjects (86%) by the IERC evaluation; these subjects were evaluable for efficacy analyses (per-protocol analysis set). All 138 subjects had ended the treatment portion of the study at the time of data cutoff for this report (13 November 2006). Ten subjects (7%) completed the protocol-specified 48 weeks of treatment and 128 subjects ended AMG 706 treatment within 48 weeks most commonly due to disease progression (60%) and adverse event (22%). A total of 78 subjects (56%) completed safety follow-up assessments (required if treated < 48 weeks) with 48 subjects (35%) who completed the assessments within the protocol-specified 14 ($\pm$ 4) days after last dose, 25 subjects (18%) > 18 days after last dose, and 5 subjects < 10 days after last dose. Fifty subjects (36%) did not complete the safety follow-up assessments. According to comments reported by the study sites, failure to complete safety follow up was most commonly due to death, hospitalization, and withdrawn consent.

Efficacy Results: Across the 120 subjects in the per-protocol analysis set (IERC-confirmed prestudy disease progression), the confirmed objective response rate (all PR per modified RECIST) was 3% (95% CI: 0.5, 7) as determined by independent review. By investigator review, the objective response rate was 1% (95% CI: 0, 5). As determined by independent review, 46% of subjects had stable disease as their best response, 33% had progressive disease, and 12% had durable stable disease (≥ 24 weeks). The Kaplan-Meier estimate of median duration of response for the responders by independent review (n = 3), was 115 days (95% CI: 113, not estimable) and median time to response was 54 days (95% CI: 50, 112). Across the 120 subjects, the Kaplan-Meier estimate of median progression-free survival time was 112 days (95% CI: 70, 162) and the median time to disease progression was 112 days (95% CI: 105, 164). As of the data cutoff date (13 November 2006), the median overall survival time was 450 days (95% CI: 345, not estimable).

Eligible subjects (per-protocol analysis set) in the PRO analysis subset who completed 4 weeks of treatment reported low scores for mean pain intensity (SD) and interference (SD) on the BPI-SF at baseline (n = 105; pain intensity: 1.75 [1.86]; pain interference: 2.03 [2.26]). After 4 weeks of treatment, no appreciable change in pain intensity or interference from baseline was reported (n = 103; mean change in pain intensity: 0.243 [1.349]; mean change in pain interference: 0.182 [1.569]). Similarly, the mean (SD) baseline EQ-5D index score (n = 104) did not change appreciably from baseline (0.75 [0.24]; Table 14-4.9.3) to 4 weeks (mean change -0.033 [0.208]). Only 8 eligible subjects in the PRO analysis subset completed 48 weeks of treatment, therefore changes in BPI-SF and EQ-5D scores from baseline to 48 weeks were not meaningful.

Final Karnofsky performance scores were the same or improved from baseline for 49% of all 138 treated subjects. For subjects in the per-protocol analysis set, the rate of subjects reporting pain on the PPI scale from the McGill Pain Questionnaire was similar at baseline and the last on-study assessment (61% vs 62%, respectively); more subjects characterized their pain as distressing at their last assessment. A palliative response (specified point reductions from baseline in the PPI scale, with no increase in opioid use) was reported for 12 subjects (10%; 95% CI: 5, 17). At study entry, 26 subjects (22%) reported baseline opioid use (8% as needed, only; 13% fixed dose); at the end of treatment, 51 subjects (43%) reported opioid use (8% as needed; 34% fixed dose).

Objective response was measured by ^{18}FDG-PET scan at week 8 (> 25% decrease from baseline in the average standardized uptake value of all RECIST target lesions). Across all 120 subjects evaluable for efficacy analyses (per-protocol analysis set), the ^{18}FDG-PET response was 23% (95% CI: 15, 31); for the 89 evaluable subjects with baseline and week-8 ^{18}FDG-PET scans, the objective response rate was 30% (95% CI: 21, 41). An association between ^{18}FDG-PET response and progression-free survival was suggested by the Cox-proportional hazards model. The model suggested that ^{18}FDG-PET responders were less likely than ^{18}FDG-PET non-responders to have disease progression (hazard ratio 0.56; 95% CI: 0.33, 0.95).

Additionally, objective response was measured using Choi response criteria at week 8 (≥ 10% decrease from baseline in the sum of longest diameter of RECIST target tumor lesion size and/or ≥ 15% decrease from baseline in average RECIST target tumor lesion density by CT scan). A total of 96 (80%) of the 120 subjects evaluable for efficacy analyses (per-protocol analysis set) were eligible for Choi assessment at week 8 (both baseline and week 8 tumor size or density measurements). The objective response by decreased tumor size was 11% (95% CI: 6, 18), by tumor density was 26% (95% CI: 18, 35), and by tumor size and/or tumor density was 33% (95% CI: 24, 42). No difference was found between Choi response and progression-free survival by the Cox-proportional hazards model; there was no difference in progression-free survival between Choi responders and Choi nonresponders (hazard ratio 0.80; 95% CI: 0.51, 1.24).

Pharmacokinetics Results: In 27 subjects who were evaluated for intensive PK analysis (intensive PK sampling on days 1 and 28: predose and postdose at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours), AMG 706 was rapidly absorbed after a single dose (day 1) and after daily

administration for 28 days (median t_{max} = 0.58 hour and 1.0 hour, respectively; n = 27). The mean C_{max}, AUC_{0-24}, and C_{24} values were slightly lower on day 28 than on day 1, indicating that there was no accumulation after daily administration. The day 28:day 1 mean ratios in the same subjects were approximately 0.89 for C_{max} (n = 27), 0.84 for AUC_{0-24} (n = 19), and 0.92 for C_{24} (n = 19) for all evaluable subjects.

A comparison of subjects with (n =19) and without prior gastrectomy (n = 8) showed similar PK results on day 1 of AMG 706 treatment. On day 28, however, the AUC and C_{24} values were slightly lower, and the mean concentration-time profile showed slightly faster elimination in the terminal phase in subjects with gastrectomy compared to those without (mean $t_{1/2,z}$ value = 4.42 hours vs 5.45 hours). Several individual AMG 706 concentration-time profiles also suggest that lower oral absorption of AMG 706 may have occurred on day 28 in subjects with gastrectomy. Measures of trough plasma AMG 706 showed no distinct trend between subjects with or without prior gastrectomy.

In subjects with available average trough PK values, there were no apparent trends between AMG 706 exposure and the occurrence of any of the treatment-emergent adverse events of interest (hypertension, diarrhea, nausea, fatigue, thromboembolic events, and gallbladder toxicities) in this study.

Safety Results: All 138 treated subjects reported ≥ 1 adverse event during the study, with diarrhea (55%), hypertension (51%), and fatigue (45%) as the 3 most common events. Other frequently reported events (≥ 20% subject incidence) included nausea (35%), headache (34%), abdominal pain (32%), anorexia (32%), vomiting (30%), weight decreased (27%), constipation (24%), and dysphonia (20%). Most adverse events (92%) were considered related to treatment. The most frequently reported grade ≥ 3 adverse events were hypertension (25%), fatigue (12%), and abdominal pain (10%). Seventy subjects (51%) had a serious adverse event, with events of abdominal pain (8%), dehydration (7%), progression of GIST (7%), hypertension (7%), and vomiting (5%) most frequently reported. Thirty-seven subjects (27%) discontinued AMG 706 treatment because of an adverse event. As of the date of data cutoff (13 November 2006), 65 subjects had died; 19 deaths occurred on study or within 30 days of last dose, and 46 deaths occurred during the long-term follow-up period. Of the 19 on-study deaths, 12 were attributed to disease progression and 7 to nondisease progression (cardiac arrest [2 events], duodenal obstruction, general physical health deterioration, myocardial infarction, pneumonia aspiration, and sepsis.). One on-study fatal event (myocardial infarction) was considered by the investigator to be related to AMG 706.

Adverse events of interest in the context of AMG 706 administration include important identified and potential risks associated with AMG 706 therapy that have been selected based on nonclinical and clinical data obtained throughout the AMG 706 development program and from the publicly-available safety profiles of other VEGFr inhibitors or multikinase inhibitors and targeted therapeutic agents. Adverse events of interest, defined as cardiac toxicity events, gallbladder toxicity events, gastrointestinal toxicity events, hematologic toxicity events, hemorrhagic events, hypertensive events (including reversible posterior leukoencephalopathy), hypothyroidism events, impaired wound healing events, pancreatic events, and thromboembolic events (arterial and venous), were reported for 88 subjects (64%). All subjects had ≥ 1 laboratory abnormality; the most common grade 3 or 4 laboratory abnormalities were increased uric acid (11%), increased glucose (8%), decreased potassium (8%), decreased sodium (7%), and decreased lymphocyte (6%) concentrations. On-study increase in blood pressure values was the only clinically significant change in vital signs; values decreased towards baseline by last assessment. Three subjects had treatment-emergent QTcB and/or QTcF interval prolongation of > 500 msec, however a definitive conclusion about QTc prolongation could not be made because of the nature of the ECG assessments (single ECGs and not centrally reviewed).

Conclusions: Data from this study of AMG 706 administered orally as 125 mg QD to subjects with imatinib-resistant GISTs, demonstrated evidence of antitumor activity after 24 weeks of

minimum follow-up. Additionally, AMG 706 had a manageable safety profile and was generally well-tolerated. The safety data appeared to be consistent with those of other small-molecule multikinase VEGFr inhibitors reported from phase 2 trials to date (Eskens and Verweij, 2006) and were generally consistent with the overall safety profile for AMG 706 monotherapy.