Product: AMG 706
Clinical Study Report: 20040273
Date: 07 March 2008

SYNOPSIS: Study 20040273

Name of Sponsor: Amgen Inc.

Name of Finished Product: Not applicable

Name of Active Ingredient: AMG 706

Title of Study: A Phase 2, Open-label Study of AMG 706 to Treat Subjects with Locally Advanced or Metastatic Thyroid Cancer

Investigators and Study Centers: This study was conducted at 42 sites in North America and Europe.

Publications based on this study:
Sherman S, Schlumberger M, Droz JP, et al. Initial results from a phase II trial of motesanib diphosphate (AMG 706) in patients with differentiated thyroid cancer (DTC) [abstract]. Proc ASCO. 2007;25(suppl 18), abstract 6017.

Schlumberger M, Elisei R, Sherman S, et al. Initial results from a phase 2 trial of motesanib disphosphate (AMG 706) in patients (pts) with medullary thyroid cancer (MTC) [abstract]. Presented at: 89th Annual Meeting of the Endocrine Society; 04 June 2007: Toronto, Canada. Available From: http://www.abstracts2view.com/endo/index.php. Abstract OR39-3. (Accessed 03 Sept 2007).

Schlumberger MJ, Sherman SI, Hoff AO, et al. Diarrhea Burden in Medullary Thyroid Cancer (MTC) Patients (pts): Impact of Motesanib Diphosphate (AMG 706) on Diarrhea Symptoms (sx) – Interim Results [abstract]. Presented at: 89th Annual Meeting of the Endocrine Society; 04 June 2007: Toronto, Canada. Available From: http://www.abstracts2view.com/endo/index.php. Abstract P3-600. (Accessed 03 Sept 2007).

Sherman S, Schlumberger M, Droz JP, et al. Initial Results from a Phase 2 Trial of AMG 706 in Patients (Pts) with Differentiated Thyroid Cancer (DTC) [abstract]. Presented at: 32nd Annual Meeting of the European Thyroid Association; 04 September 2007: Leipzig, Germany. Horm Res 2007;68(suppl 3):2-20. (Accessed 03 Sept 2007).

Sherman SI, Schlumberger MJ, Elisei R, et al. Exacerbation of postsurgical hypothyroidism during treatment of thyroid carcinoma with motesanib disphosphate (AMG 706) [abstract]. Presented at: 89th Annual Meeting of the Endocrine Society; 04 June 2007: Toronto, Canada. Available From: http://www.abstracts2view.com/endo/index.php. Abstract P3-587. (Accessed 03 Sept 2007.

Schlumberger M, Elisei R, Sherman S, et al. Initial Results from a Phase 2 Trial of AMG 706 in Patients (Pts) with Medullary Thyroid Cancer (MTC) [abstract]. Presented at: 32nd Annual Meeting of the European Thyroid Association; 05 September 2007: Leipzig, Germany. Horm Res 2007;68(suppl 3):2-20. (Accessed 03 Sept 2007).

Pacini F, Sherman SI, Schlumberger MJ, et al. Exacerbation of postsurgical hypothyroidism during treatment of advanced differentiated (DTC) or medullary (MTC) thyroid carcinoma with AMG 706 [abstract]. Presented at: 32nd Annual Meeting of the European Thyroid Association; 01-05 September 2007: Leipzig, Germany. Horm Res 2007;68(suppl 3):21-91. (Accessed 03 Sept 2007).

Baudin E, Schlumberger M, Sherman S, et al. Diarrhea Burden in Medullary Thyroid Cancer (MTC) Patients (pts) with Medullary Thyroid Cancer: Impact of AMG 706 on Diarrhea Symptoms (sx) – Interim Results [abstract]. Presented at: 32nd Annual Meeting of the European Thyroid Association; 01-05 September 2007: Leipzig, Germany. Horm Res 2007;68(suppl 3):21-91.

Study Period: 29 July 2005 (first subject enrolled) to 07 February 2007 (last subject end-of-study visit); long-term follow up (LTFU) continues for up to 5 years.

Development Phase: 2

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Introduction and Objectives: Thyroid cancer is an uncommon malignancy that represents approximately 1% to 2% of malignancies occurring annually in the United States (Figge, 1999). The most common types of thyroid cancer arise from follicular cells and are referred to collectively as differentiated thyroid cancers (DTCs). If detected early, most DTCs can be successfully managed by total thyroidectomy, radioiodine (RAI) therapy, levothyroxine as an adjunct therapy to surgery and RAI therapy (in the management of thyrotropin-dependent well-differentiated thyroid cancer), and external beam radiotherapy (Ahuja and Ernst, 1987). For patients with local recurrences or metastatic thyroid cancer, however, the only approved treatment option (in addition to continued thyroid stimulating hormone suppression) is doxorubicin (Adriamycin® [doxorubicin hydrochloride] Prescribing Information, 2006), which is not generally used in medical practice for thyroid carcinoma due to inconsistent response rates and severe toxicities (Shimaoka et al, 1985; Ahuja and Ernst, 1987; Droz et al, 1990). Furthermore, 40% to 50% of patients with distant metastases will die of thyroid cancer within 5 years (Mazzaferri and Jhiang, 1994; Hundahl et al, 1998). These data indicate that locally advanced or metastatic thyroid cancer is a serious and life-threatening disease for which there is no adequate treatment, and that an unmet medical need exists for patients with this disease.

Medullary thyroid cancer (MTC) is a rare histologic subtype of thyroid cancer. It represents roughly 3% to 5% of all thyroid cancer cases (Hundahl et al, 1998) and has a 10-year survival rate of approximately 65% to 80% (Duh et al, 1989). Total thyroidectomy is indicated in all subjects with MTC and is sometimes followed by external beam radiotherapy. Distant metastases are the main cause of MTC-related death and the 5-year relative survival rate for subjects with stage IV MTC is 40% (Hundahl et al, 1998). Systemic chemotherapy (single agent and combination) has been used to treat distant metastases, but as with DTC, its effectiveness in MTC has not been consistent and it is associated with severe toxicities (Nocera et al, 2000; Schlumberger et al, 1995; Sherman, 2006). Given the inconsistent benefit and significant toxicities of chemotherapy for patients with locally advanced or metastatic MTC, an unmet medical need exists for patients with this disease.

AMG 706 is a highly selective, orally active inhibitor of angiogenesis with direct antitumor activity. It inhibits vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR-1, VEGFR-2, and VEGFR-3), and 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).

The primary objective of this study was to determine the effect of AMG 706 on the objective response rate (complete response and partial response) in subjects with locally advanced or metastatic thyroid cancer in each of 2 strata: DTC and MTC. The secondary objectives of this study were to determine the effect of AMG 706 on duration of response, tumor-related symptoms (MTC only), and progression-free survival time in each stratum. Additionally, the safety profile of AMG 706 for subjects in each stratum was to be assessed.

Methodology: Eligible subjects were treated orally with 125 mg of AMG 706 once daily for up to a maximum of 48 weeks (study day 1 to the end of week 48) until evidence of disease progression, death, or unacceptable toxicity, whichever occurred first. Upon treatment discontinuation, subjects were to be followed until evidence of disease progression, death, or unacceptable toxicity, whichever occurred first (if the subject did not have an assessment of disease progression during the treatment period) and survival until death or for up to 5 years after study day 1.

Radiological assessment of tumors was to be performed at screening, after 7 weeks of AMG 706 treatment, and every 8 weeks thereafter or when disease progression was suspected. Radiological tumor assessments were reviewed by an independent central radiographic facility for determination of tumor response based on modified Response Evaluation Criteria for Solid Tumors (RECIST). Tumor response based on investigator review was also assessed. Subjects

with MTC were asked to complete a MTC-related symptoms questionnaire at baseline**,** after 7 weeks of AMG 706 treatment, and every 8 weeks thereafter. Subject treatment was based on investigator read and other assessments.

This report details results from analyses performed when all subjects had been followed for at least 48 weeks after the first dose of AMG 706 or had completed the end-of-treatment assessments.

Number of Subjects Planned: Approximately 160 subjects (80 DTC, 80 MTC) were planned.

Number of Subjects Enrolled: A total of 227 subjects were screened for this study and 184 subjects were subsequently enrolled. Of the 184 enrolled subjects, 93 subjects were enrolled in the DTC stratum and 91 subjects were enrolled in the MTC stratum.

		DTC	MTC
Sex:	females	44 (47%)	32 (35%)
	males	49 (53%)	59 (65%)
Age: (years)	median (range)	62 (36, 81)	49 (18, 77)
Ethnicity (Race):	white	85 (91%)	86 (95%)
	Asian	4 (4%)	1 (1%)
	Hispanic	3 (3%)	4 (4%)
	black	1 (1%)	0 (0%)

Diagnosis and Main Criteria for Eligibility: The following are key criteria to be met to be eligible for this study:

- ≥ 18 years old
- provided written informed consent
- histologically confirmed locally advanced or metastatic thyroid cancer (excluding undifferentiated/anaplastic thyroid cancer and thyroid lymphomas)
- presence of at least 1 measurable lesion by modified RECIST (not previously radiated)
- Eastern Cooperative Oncology Group (ECOG) 0 to 2 score
- systolic blood pressure ≤ 145 mm Hg and diastolic blood pressure ≤ 85 mm Hg (antihypertensive therapy to achieve these parameters was allowable)

In addition, subjects with DTC must have had documented evidence of disease progression by modified RECIST within 6 months of study day 1, and the disease must not have been amenable to or refractory to surgical resection, external beam radiation therapy, RAI therapy, or other local therapies. Subjects with MTC must have had either documented evidence of disease progression within 6 months of study day 1 or symptomatic disease at the time of screening in the absence of disease progression. The disease must not have been amenable to or refractory to surgical resection, external beam radiation therapy, or other local therapies. Subjects must have had measurable disease at baseline.

Subjects were to be excluded from the study (screen failures) if they met any of the following criteria:

- untreated or symptomatic brain metastases
- prior malignancy (other than thyroid cancer, in situ cervical cancer, or basal cell cancer of the skin), unless treated with curative intent and without evidence of disease for ≥ 3 years before study day 1
- myocardial infarction or unstable or uncontrolled disease or condition related to or impacting cardiac function within 1 year before study day 1
- arterial thrombosis, deep vein thrombosis, or pulmonary embolism within 1 year before study day 1
- history of hemoptysis within 6 months of study day 1

- evidence of transmural invasion into the trachea or esophagus, or circumferential involvement of carotid or jugular vessels at the time of screening before study day 1
- previous exposure to AMG 706 or other tyrosine kinase inhibitors of RET or VEGF receptors
- ongoing treatment with any therapy containing St. John's Wort, coumarin anticoagulants, rifampin, phenobarbital, ketoconazole, itraconazole, clarithromycin, erythromycin, grapefruit (ie, whole fruit or fruit juice), any human immunodeficiency virus (HIV) protease inhibitors, cyclosporine, tacrolimus, or nefazodone
- treatment with anticancer therapy within 30 days of study day 1, including chemotherapy, retinoid therapy, radiation therapy, or hormonal therapy for thyroid cancer other than chronic thyroid stimulating hormone suppression

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 706 was self-administered orally once daily as one 25-mg tablet and one 100-mg tablet for a total daily dose of 125 mg.

Duration of Treatment: The planned treatment duration was 48 weeks, followed by monitoring of disease progression (for subjects without evidence of disease progression at end of study) and survival until death or for up to 5 years after study day 1. After 48 weeks of therapy, subjects receiving continued clinical benefit from AMG 706 were eligible to continue treatment in an extension study (Amgen Study 20050130).

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

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Study Endpoints: Endpoints for each stratum were assessed independently.

Efficacy: The primary efficacy endpoint of this study was the objective response rate (complete response and partial response) as defined by modified RECIST and assessed per independent review. Secondary efficacy endpoints were duration of response and progression-free survival time for both DTC and MTC, as well as tumor-related symptoms for MTC.

Safety: incidence of treatment-emergent adverse events

Pharmacokinetic: AMG 706 pharmacokinetic parameters (maximum observed plasma concentration after dosing [C_{max}], estimated half-life [$t_{½}$], area under the concentration-time curve from time 0 to 24 hours [AUC_{0-24}], and trough plasma concentration at 24 hours postdose [C_{24}])

Other: time to response, overall survival time, patient-reported outcomes (PRO), and changes in tumor markers

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Statistical Methods: All analyses were done separately for each stratum. Descriptive statistics were provided for the efficacy, safety, pharmacokinetic and patient-reported outcomes endpoints. Response information was provided by the investigator and by an independent review of tumor images. Each efficacy endpoint was derived based on the response information provided by each entity. Each efficacy endpoint was analyzed based on independent review and based on investigator review of the efficacy data. Descriptive statistics were also provided for demographics, baseline disease characteristics, vital signs, and laboratory parameters. Where appropriate, continuous measurements were summarized using the following summary statistics: mean, standard deviation, median, interquartile range, range, and number of subjects. For discrete data, the frequency and proportions were provided. Point estimates of time-to-event endpoints (eg, survival, progression-free survival) were accompanied by 2-sided 95% confidence interval (CI) for overall response.

Per protocol, an interim analysis for Study 20040273 was conducted after the first 28 subjects in each stratum who were still receiving AMG 706 treatment completed their week 16 computed tomography (CT) or magnetic resonance imaging (MRI) scans. The primary purpose of this interim analysis, as originally stated in the protocol, was to determine whether to continue full enrollment into each stratum. Because full enrollment of each stratum occurred before the planned, protocol-specified interim analysis, a trial integrity document (on file at Amgen) was

created before the interim analysis, which blinded the study team to the details of the planned interim analysis results to help reduce the risk of operational bias. The outcome of the interim analysis was that there was evidence of efficacy as defined in the protocol and the safety profile of AMG 706 was deemed acceptable to continue the study.

Summary of Results:

Subject Disposition: A total of 227 subjects were screened for this study and 184 subjects were subsequently enrolled. Of the 184 enrolled subjects, 93 subjects were enrolled in the DTC stratum and 91 subjects were enrolled in the MTC stratum. All 93 subjects (100%) enrolled in the DTC stratum and all 91 subjects (100%) enrolled in the MTC stratum received at least 1 dose of AMG 706 and were included in the full analysis set.

DTC Stratum: Of the 93 subjects enrolled in the DTC stratum, 32 (34%) completed the study in accordance with protocol-specified criteria. Of the 61 subjects who ended the study for reasons other than protocol-specified criteria, the most common reason was disease progression (36 subjects [39%]), while 10 subjects (11%) discontinued study due to an adverse event, 6 subjects (6%) discontinued study due to death, and 2 subjects (2%) discontinued study due to withdrawal of consent. Eight subjects (9%) in the DTC stratum died within 30 days of last AMG 706 administration: 4 due to progressive disease, 2 due to pulmonary hemorrhage, 1 due to acute respiratory distress (suspected pulmonary embolus), and 1 due to cardio-respiratory distress; only the pulmonary hemorrhage events were considered by the investigator to be treatment related. At the time of analysis, 19 subjects died during the LTFU (ie, $>$ 30 days after the last AMG 706 administration).

MTC Stratum: Of the 91 subjects enrolled in the MTC stratum, 37 (41%) completed the study in accordance with protocol-specified criteria. Of the 54 subjects who ended the study for reasons other than protocol-specified criteria, 30 subjects (33%) discontinued study due to disease progression, 10 subjects (11%) discontinued study due to an adverse event, 5 subjects (5%) discontinued study due to death, 3 subjects (3%) discontinued study due to withdrawal of consent, and 2 subjects (2%) discontinued study due to determination of ineligibility. Seven subjects (8%) in the MTC stratum died within 30 days of last AMG 706 administration: 1 was due to progressive disease, 3 were due to medullary thyroid cancer, 1 was due to thyroid gland cancer, 1 was due to lung metastases, and 1 was due to hepatic failure; none were considered by the investigator to be treatment related. At the time of analysis, 17 subjects died during the LTFU (ie, $>$ 30 days after the last AMG 706 administration).

Efficacy Results:

DTC Stratum: In this study, with a median follow-up of approximately 11.5 months (50 weeks), the overall response rate (complete and partial responses per modified RECIST) for subjects in the DTC stratum (n = 93) was 14% (95% CI: 7.7, 22.7) for the full analysis set as determined by independent central review. The overall response rate based on the investigator assessments also was 14% (95% CI: 7.7, 22.7). As determined by independent central review, 62 subjects (67%) achieved stable disease, with 33 subjects (35%) having durable stable disease ($\geq$ 24 weeks). As determined by independent central review, the median duration of response was approximately 7.4 months (225 days), with 5 of the 13 subjects who had an objective response relapsed. The median time to response was approximately 3.5 months (105 days). The Kaplan-Meier estimate of the median progression-free survival time was approximately 9.1 months (277 days; 95% CI: 221, 351). The Kaplan-Meier estimate of median overall survival time was not estimable.

MTC Stratum: In this study, with a median follow-up of approximately 11.3 months (49 weeks), 2 subjects (2%) in the MTC stratum (n = 91) had a partial response (per modified RECIST) as determined by independent central review. One of the 2 responders maintained tumor burden reduction at the time of the analysis and 1 relapsed. The overall response rate based on the investigator read of the radiographic images was 9% (95% CI: 3.9, 16.6). As determined by independent central review, 74 subjects (81%) achieved stable disease, with 44 subjects (48%) having durable stable disease ($\geq$ 24 weeks). The duration of response for the responder who

relapsed was approximately 4.8 months; the time to response for each of the 2 responders was 2.3 months (71 days) and 3.4 months (105 days). The Kaplan-Meier estimate of median progression-free survival time was approximately 10.9 months (333 days; 95% CI: 301, 389). The Kaplan-Meier estimate of median overall survival time was not estimable.

Safety Results:

DTC stratum: All DTC subjects had at least 1 treatment-emergent adverse event during the study, with diarrhea (75%) as the most frequently reported adverse event. Other frequently reported adverse events (ie, subject incidence ≥ 20%) for subjects in the DTC stratum included fatigue (60%), hypertension (58%), headache and weight decreased (46%), abdominal pain (42%), nausea (41%), anorexia (38%), dyspnea (25%), and cough and vomiting (each 22%). Grade 3, 4, or 5 adverse events were reported for 73 subjects (78%). The most frequently reported grade 3/4/5 events (≥ 10%) by preferred term were hypertension for 25 subjects (27%), diarrhea for 13 subjects (14%), and dyspnea for 9 subjects (10%).

Of the 93 subjects in the DTC stratum, 87 subjects (94%) had adverse events considered by the investigator to be possibly related to treatment with AMG 706, while 22 subjects (24%) had an adverse event leading to discontinuation of treatment. Thirty-five subjects (38%) had serious adverse events; acute cholecystitis (5%), dyspnea (4%), hypertension (4%), abdominal pain (4%), nausea (4%), thyroid gland cancer (4%), hypocalcemia (3%), pulmonary hemorrhage (3%), and vomiting (3%) were the most frequently reported. Serious, treatment-related events were reported for 19 subjects (20%); acute cholecystitis (4%), hypertension (4%), and nausea (3%) were the most frequently reported. Eight subjects (9%) had a fatal adverse event within 30 days of last AMG 706 administration.

Adverse events of interest included hypertensive events, thromboembolic events, hemorrhagic events, gallbladder toxicity, pancreatitis events, hypothyroidism events, cardiac toxicity, hematologic toxicity, proteinuria events, gastrointestinal perforation, pancreatitis, cardiac toxicity, reversible posterior leukoencephalopathy syndrome (RPLS), and impaired wound healing. The combined subject incidence rate of these 12 categories of adverse events was 82%; the incidence of these adverse events that were considered treatment related was 70%. Hypertensive adverse events, most of which were considered by the investigator to be possibly related to treatment with AMG 706, were reported for 54 subjects (58%) and were the most frequently reported adverse events of interest; 25 subjects (27%) had grade 3 hypertension.

No clinically significant changes in electrocardiogram (ECG) parameters, laboratory values, or vital signs (except for blood pressure) were observed. Of the 8 deaths on study, 4 were attributed to disease progression. There were 4 non-disease progression, on-study deaths: 2 due to pulmonary hemorrhage, 1 due to cardio-respiratory arrest, and 1 due to acute respiratory distress; only the pulmonary hemorrhage events were considered by the investigator to be treatment related.

MTC stratum: Of the 91 subjects in the MTC stratum, 90 (99%) had at least 1 treatment-emergent adverse event during the study, with diarrhea for 52 subjects (57%) as the most frequently reported adverse event. Other frequently reported adverse events (ie, subject incidence ≥ 20%) for subjects in the MTC stratum included fatigue for 43 subjects (47%), nausea for 31 subjects (34%), hypothyroidism for 30 subjects (33%), anorexia for 29 subjects (32%), abdominal pain for 27 subjects (30%), hypertension for 26 subjects (29%), weight decreased for 25 subjects (27%), and headache for 24 subjects (26%). Grade 3, 4, or 5 adverse events were reported for 54 subjects (59%). The most frequently reported (≥ 5%) grade 3/4/5 events by preferred term were diarrhea (15%), hypertension (12%), and fatigue (9%).

Of the 91 subjects in the MTC stratum, 80 subjects (88%) had adverse events considered by the investigator to be possibly related to treatment with AMG 706, while 12 subjects (13%) had an adverse event leading to discontinuation of treatment. Twenty-six subjects (29%) had serious adverse events, with abdominal pain, acute cholecystitis, dyspnea, medullary thyroid cancer, and pneumonia (3% each) as most frequently reported serious adverse events. Serious, treatment-related adverse events were reported for 8% of subjects and included acute cholecystitis,

asthenia, abdominal pain, cholelithiasis, fecal incontinence, hypocalcemia, paraplegia, and urinary incontinence. Five subjects (5%) had a fatal adverse event within 30 days of last AMG 706 administration; 2 other deaths that occurred within 30 days of last AMG 706 administration were reported but were not attributed to an adverse event.

The combined subject incidence rate of the 12 categories of adverse events of interest was 65%; the incidence of these adverse events that were considered treatment related was 56%. Hypertensive adverse events, most of which were considered by the investigator to be possibly related to treatment with AMG 706, were reported for 27 subjects (30%); 11 subjects (12%) had grade 3 hypertension.

No clinically significant changes in ECG parameters, laboratory values, or vital signs (except for blood pressure) were observed. Of the 7 deaths on study, 1 was due to progressive disease, 3 were due to medullary thyroid cancer, 1 was due to thyroid gland cancer, 1 was due to lung metastases, and 1 was due to hepatic failure; none were considered by the investigator to be treatment related.

Pharmacokinetic Results: Nineteen subjects had blood samples collected for intensive pharmacokinetic analyses (9 DTC subjects and 10 MTC subjects). After single-dose oral administration (day 1), AMG 706 was rapidly absorbed, with median time to maximum plasma concentration (t_{max}) values of 1.0 hour for DTC subjects and 0.73 hour for MTC subjects. Mean C_{max}, AUC, and C_{24} values were higher in DTC subjects than in MTC subjects, with percent difference values ranging from 25% to 81%. Furthermore, the mean apparent clearance (CL/F) value in DTC subjects was approximately half of that observed in MTC subjects. Between week 4 and week 24, predose AMG 706 trough plasma concentrations (C_{min}) after 125 mg daily administration had median values ranging from 8 to 26 ng/mL in DTC subjects and from 5 to 7 ng/mL in MTC subjects. At each scheduled time point, median C_{min} values were higher (percent difference values ranging from 33% to 74%) in subjects with DTC than in subjects with MTC. The median C_{min} values for all subjects were higher than the 50% inhibitory concentration (IC_{50}) value (4 ng/mL) but lower than the 90% inhibitory concentration (IC_{90}) value (28 ng/mL) estimated by the in vitro human umbilical vein endothelial cell (HUVEC) method.

Patient-reported Outcomes Results:

Medullary Thyroid Cancer-related Symptoms Questionnaire (MTCRSQ): The MTCRSQ was administered to the MTC subjects. Medullary MTCRSQ results indicate that subjects with diarrhea at baseline (diarrhea subgroup) reported an initial decrease in mean diarrhea episodes / day (5.2 at baseline to 3.9; p=0.002) and in diarrhea severity (42.7 to 56.4; 0-100 scale; 100 least severe; p=0.027) and a trend toward less interference (65.9 to 71.5; 0-100 scale; 100 least severe; p=0.064) at week 16; however, this was not sustained in the subjects who provided data out to week 48. Subjects with no diarrhea at baseline reported mild diarrhea symptoms after initiating AMG 706, which is consistent with the known side-effect profile of AMG 706.

European quality of life utility scale (EQ-5D): No meaningful changes in either the EQ-5D health utilities index or visual analog scores were observed over time in either the DTC or MTC stratum.