AMG 706 FIRST IN HUMAN, OPEN-LABEL, DOSE-FINDING STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS (PK) IN SUBJECTS WITH ADVANCED SOLID TUMORS

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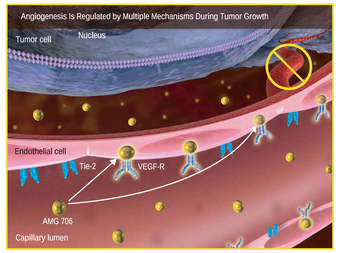
ABSTRACT

Introduction: AMG 706 is a potent and selective small molecule inhibitor of multiple kinases, including vascular endothelial growth factor receptors, platelet derived growth factor receptor, Ret, and c-kit. To assess the safety, establish the maximum tolerated dose, and generate PK profiles of oral AMG 706, a clinical study in adult subjects was initiated. *Methods*: Individuals with advanced solid tumors, refractory to standard therapy or with no standard therapy available, were enrolled in this on-going, open-label, dose-escalation study. Cohorts of 3 to 9 subjects were orally administered 50, 100, 125, or 175 mg once daily (QD) or 25 mg twice daily (BID) for 21 days in a 28-day cycle. Additional cohorts were enrolled to 125 mg QD in a continuous dosing regimen and a tablet formulation. Subjects remained on study until tumor progression or unacceptable toxicities occurred. *Results*: AMG 706 was generally well-tolerated up to 125 mg QD using the intermittent dose schedule. Most adverse events were mild to moderate in severity and reversible. Thirty-four of the 43 treated subjects reached the day 50 tumor assessment, revealing 2 (leiomyosarcoma, thyroid) partial response, 4 (gastrointestinal stromal, thyroid, breast, and carcinoid tumors) minor responses (-8% to -29% in the sum of the longest diameter of target lesions), and an additional 14 stable diseases (SD). Six subjects maintained SD for at least 134 days and 3 of these 6 subjects had SD for more than 218 days on study. AMG 706 demonstrated favorable exposure and half-life (about 7 hrs) at all dose levels. A single- (and multiple) dose PK result comparison suggests that no significant accumulation of AMG 706 occurred during the first 3 weeks of drug administration. *Conclusions*: AMG 706 appears to be safe and tolerable at daily doses up to 125 mg. Once daily dosing generated sustained exposure sufficient to elicit partial, minor and SD responses across multiple cancer types, suggesting that AMG 706 has broad anti-tumor activity.

INTRODUCTION

AMG 706 is a potent, oral, multi-kinase small molecule inhibitor that exhibits anti-angiogenic and anti-tumor activity by selectively targeting all known VEGF receptors, PDGF receptors, c-kit, and Ret.

The aim of this study was to evaluate the safety, tolerability, and PK parameters of AMG 706 in subjects with advanced solid tumors that were refractory to standard treatment or for which no standard therapy was available.



AMG 706 Selectively Inhibits a Subset of Kinases

Receptor Kinase	Inhibition (IC_{50} nM)
VEGF-R1	2
VEGF-R2	3
VEGF-R3	6
RET	91
c-Kit	8
PDGF-R*	207
47 other kinases are not inhibited by AMG 706	

*represents IC_{50} in nM in cell-based assays

STUDY DESIGN AND SUBJECTS

Primary Objective

- To assess the safety, establish the maximum tolerated dose (MTD), and generate PK profiles of AMG 706 after oral administration

Secondary Objectives

- To assess safety profiles with significant laboratory changes and adverse events not defined as dose limiting toxicities
- To determine the pharmacodynamic profile of AMG 706 in study subjects by measuring tumor vascular permeability using dynamic contrast enhanced-magnetic resonance

Study Design

- Phase 1, first in human, 2 center, open-label study
- Cohorts of 3 to 9 subjects received AMG 706 on an intermittent (daily for 3 weeks, followed by a week free of AMG 706) or continuous (daily without the AMG 706-free period) dosing schedule
- 50 (N = 3), 100 (N = 6), 125 (N = 9), 175 (N = 6) mg QD and 25 (N = 7) mg BID intermittently
- A cohort of 125 mg QD continuous dosing continues to accrue subjects
- Subjects were considered eligible for the study if they met the following criteria:
  - Pathologically documented, advanced solid tumor that was refractory to standard treatment or for which no standard therapy was available
  - ≥ 18 years of age with a life expectancy ≥ 3 months
  - Eastern Cooperative Oncology Group performance status ≤ 2
  - Absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, or hemoglobin ≥ 10 g/dL
- Subjects were excluded from study participation if they met the following criteria:
  - Inadequate organ or laboratory function
  - Hematological malignancies, history of hypercoagulopathy, or history of bleeding diathesis
  - Tumors with central nervous system involvement
  - Prior treatment with a tyrosine kinase inhibitor of VEGF
  - Required use of anticoagulation therapy

ASSESSMENTS

Tolerability

- Subjects remained on study until tumor progression or unacceptable toxicities occurred
  - Adverse events were graded using the Common Terminology Criteria for Adverse Events (v 3.0)
  - Dose limiting toxicities (DLT) were defined as any related grade 3 or 4, or severe hematological or nonhematological toxicity, during the initial 28 days of study
  - MTD was defined as the highest dose level with an observed incidence of a DLT in < 33% of the subjects enrolled in the cohort

Pharmacokinetics

- PK profiles for AMG 706 were obtained after a single dose on study day 1 and after multiple doses on study day 21

Efficacy

- Tumor response was assessed using a modified RECIST criteria at week 8 and every 12 weeks thereafter

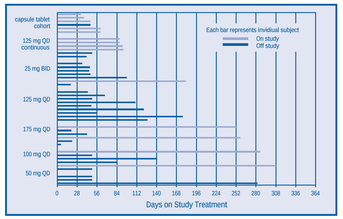
RESULTS

Subject Demographics

- Forty-three subjects were enrolled and received at least one dose of AMG 706 with the time on treatment ranging from 1 to 285 days

Total subjects, N	43
Evaluable for safety, n	43
Evaluable for tumor response, n	34
Sex, n (%)	
Men	17 (40%)
Women	26 (60%)
Race	
Caucasian	40 (93.0%)
Other	3 (7%)
Mean age, years (range)	57(25 to 81)
ECOG performance status, n (%)	
0	10 (23%)
1	33 (77%)
Primary Cancer Site, n (%)	
Colorectal	6 (14%)
Sarcoma	5 (12%)
Breast	4 (9%)
GIST	4 (9%)
Ovarian	4 (9%)
Thyroid	4 (9%)
NSCLC	4 (9%)
Other	12 (28%)

Treatment Duration (20 July 2004)



Study Clinical Experience

Cohort	Dose Level	Enrolled	Related SAE	DLT	Day 50 Response Evaluation	Best Response
I	50 mg QD	3	0	0	3	PR (1)
II	100 mg QD	6	0	0	6	MR* (1); SD (3)
III	175 mg QD	6	2	3	4	PR (1); MR* (1)
IV	125 mg QD	9	1	1	8	MR* (1); SD (4)
V	25 mg BID	7	0	0	6	SD (2)
VI	125 mg QD continuous#	6	0	0	5	MR* (1); SD (3)
VII	capsule tablet study	6	0	0	2	SD (2)
		43	3	4	34	PR (2); MR* (4) SD (14); PD (14)

For continuous dosing, cycle 1 consists of 28 days; * MR = minor response (- 8 to -29% SLD)

EFFICACY

- Thirty-four of the 43 treated subjects reached the day 50 tumor assessment, with 2 partial responses (leiomyosarcoma, thyroid), 4 minor responses (gastrointestinal stromal, thyroid, breast, and carcinoid tumors) (-8% to -29% in the sum of the longest diameter of target lesions), and an additional 14 stable diseases
- Six of 14 subjects with SD maintained SD for at least 134 days and 3 of these 6 subjects had SD for more than 218 days on study

SAFETY AND TOLERABILITY

- More than half (58%) of the subjects did not experience a serious adverse event (SAE) or DLT
- Thirty-one subjects (72%) experienced treatment-related adverse events, most of which were mild to moderate in severity
- The most frequent adverse events considered possibly related to AMG 706 were fatigue (35%) and headache (23%)

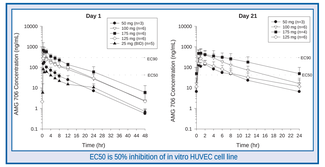
Serious Adverse Events and Dose Limiting Toxicities (20 July 2004)

Dose Group	Subject Number	Event Type	Event	Criteria	Relationship
25 mg BID	2013	SAE	Progressive Disease	Fatal: off study	No
	2014	SAE	Respiratory Syncitial Virus	Hospitalization	No
	2020	SAE	Anemia	Hospitalization	No
50 mg QD	1001	SAE	Abdominal Surgery	Hospitalization	No
100 mg QD	1004	SAE	Progressive ovarian cancer	Hospitalization	No
	2004	SAE	Cholecystitis*	Hospitalization	No
125 mg QD	1010	SAE	G3 Hypertension	Hospitalization	Yes
	2010	DLT	G3 Creatinine, G4 Hyponatremia	Dose reduction to 50 mg QD	Yes
	2011	SAE	Infection	Hospitalization	No
	2012	SAE	Pulmonary Embolus	Fatal: off study	No
	2021	SAE	Confusion	Hospitalization	No
125 mg QD	2024	SAE	Bowel Obstruction	Hospitalization	No
	2022	SAE	Collapsed Lung	Hospitalization	No
175 mg QD	1006	SAE/DLT	Dehydration, Elevated Bilirubin	Hospitalization	Yes
	1007	SAE/DLT	Encephalopathy, Colitis, Hypertension	Hospitalization	Yes
	2006	SAE	Progressive Disease	Fatal: off study	No
	2007	DLT	G3 Fatigue	Dose reduction to 100 mg QD	Yes
	2008	SAE	Abdominal Mass Resection	Hospitalization: off study	No
	2009	SAE	Abdominal Pain, Emesis	Hospitalization	No
	2009	SAE	Confusion	Hospitalization	No

No Significant Accumulation of Drug Occurs During the First 3 Weeks of AMG 706 Administration

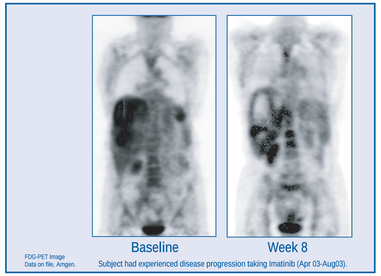
PK Parameter	Day 1 125 mg (n = 6)	Day 21 125 mg (n = 6)
C_{max} (ng/mL)	417 ± 92	425 ± 249
$t_{1/2}$ (hr)	6.98 ± 1.92	5.05 ± 2.24
AUC_{0-24} (µg•hr/mL)	2.84 ± 0.99	1.55 ± 0.96
CL/F (L/hr)	50.1 ± 22.2	101 ± 43
C_{24} (ng/mL)	29.3 ± 21.9	11.7 ± 12.9

Preliminary Mean AMG 706 Concentrations



EC50 is 50% inhibition of in vitro HUVEC cell line

Subject 2009, a 63 year old Caucasian woman with Imatinib-resistant GIST, started on AMG 706 175 mg QD (Nov03) and demonstrated reduction of metabolic activity on ^{18}FDG-PET (Dec 03).



CONCLUSIONS

- AMG 706 was generally well tolerated as monotherapy in subjects with advanced solid tumors
- AMG 706 125 mg QD continuous oral dosing is recommended for further investigation in future studies
- AMG 706 demonstrated activity in subjects with a number of different tumor types with:
  - Partial and minor responses in leiomyosarcoma, thyroid, imatinib-resistant GIST, breast, and carcinoid tumors
  - Stable disease in renal cell carcinoma, sarcoma, NSCLC, ovarian, and other tumors
- PK profiles established sustained exposure and a sufficient half-life for convenient, once-daily dosing
- Continued study in more homogeneous subject populations and with other anti-tumor agents will identify the optimal disease settings for AMG 706 use

AMGEN

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