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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INTRODUCTION

AMG 706 is a potent, oral, multi-kinase small molecule inhibitor that inhibits angiogenic and tumor growth activity by selectively targeting all known VEGF receptors, PDGF receptor, and FGFR receptor. 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 treatment was available.

STUDY DESIGN AND KINASES

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 profiles of AMG 706 in study subjects by measuring tumor vascular permeability using dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI) and tumor growth

Study Design
- Phase 1: First in human, 2 center, open label study
- Cohorts of 3–6 subjects received escalating doses of AMG 706 (125, 200, 500 mg QD) and PK profiles were established at all dose levels
- A cohort of 125 mg QD continuous dosing continues to accrue subjects

RESULTS

Subject Demographics
- Forty-three subjects were enrolled and received at least one dose of AMG 706 with the time on treatment ranging from 14 to 255 days

ASSESSMENTS

Tolerability
- Subjects remained on study until tumor progression or unacceptable toxicities occurred
- Most adverse events were mild to moderate in severity and reversible
- Thirty-four of the 43 treated subjects reached the day 50 tumor assessment

Efficacy
- Thirty-four of the 40 treated subjects reached the day 50 tumor assessment, with 2 partial responses (NSCLC, renal cell carcinoma), 4 minor responses (gastrointestinal stromal tumor, breast, and carcinoid tumors) and 10 stable disease (SD). Eighteen subjects demonstrated SD for >125 days and 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 (76%) 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 (28%) and headache (23%)

CONCLUSIONS

- AMG 706 was generally well tolerated as monotherapy in subjects with advanced solid tumors
- AMG 706 125 mg QD continuous dosing is recommended for further investigation in future studies
- AMG 706 demonstrated activity in subjects with a variety of different tumor types with:
  - Partial or minor responses 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 dose dependent exposure and half-life (about 7 hrs) at all dose levels

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

Primary objective: To determine the pharmacodynamic profile of AMG 706 in subjects with advanced solid tumors, refractory to standard therapy or with no standard therapy available, were enrolled in this open-label, dose-escalation study. Cohorts of 3-6 subjects were administered 38, 125, 175, or 200 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 (pancreatic, thyroid) partial responses, 4 (gastrointestinal stromal, thyroid, breast, and carcinoid) tumor minor responses (8% to 29% in the sum of the longest diameter of target lesions), and an additional 14 stable disease (SD). Six subjects maintained SD for at least 124 days and 3 of these 6 subjects had SD for more than 218 days on study. AMG 706 demonstrated favorable tolerability and PK parameters of AMG 706 in subjects with advanced solid tumors, refractory to standard therapy or with no standard therapy available, were enrolled in this open-label, dose-escalation study. Cohorts of 3-6 subjects were administered 38, 125, 175, or 200 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 (pancreatic, thyroid) partial responses, 4 (gastrointestinal stromal, thyroid, breast, and carcinoid) tumor minor responses (8% to 29% in the sum of the longest diameter of target lesions), and an additional 14 stable disease (SD). Six of the 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. AMG 706 demonstrated safety and tolerability at daily doses up to 125 mg QD. Once daily dosing generated sustained exposure and half-life (about 7 hrs) at all dose levels. A single (and multiple) dose PK result comparison suggests exposure and half-life (about 7 hrs) at all dose levels. A single (and multiple) dose PK result comparison suggests exposure and half-life (about 7 hrs) at all dose levels.