An International, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of AMG 479 with Exemestane or Fulvestrant in Postmenopausal Women with Hormone Receptor Positive Locally Advanced or Metastatic Breast Cancer

AMG 479
Amgen Protocol Number 20060362

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Date: **Amendment 2, 01 June 2011**
Date: Amendment 1, 03 April 2008
Date: 14 November 2007
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Investigator's Agreement

I have read the attached protocol entitled An International, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of AMG 479 with Exemestane or Fulvestrant in Postmenopausal Women with Hormone Receptor Positive Locally Advanced or Metastatic Breast Cancer dated **Amendment 2, 01 June 2011** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and local ethics and/or institutional review board regulations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Principal <<*or Coordinating*>> Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: An International, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of AMG 479 with Exemestane or Fulvestrant in Postmenopausal Women with Hormone Receptor Positive Locally Advanced or Metastatic Breast Cancer

Study Phase: 2

Indication: Postmenopausal women with hormone receptor (HR)-positive, locally advanced or metastatic breast cancer who have disease progression during or within 12 months after completing prior adjuvant endocrine therapy or during the first prior endocrine therapy for metastatic disease

Primary Objective: To provide an estimate of the relative efficacy of Arm A (AMG 479 in combination with endocrine therapy [exemestane or fulvestrant] versus Arm B (AMG 479 placebo in combination with endocrine therapy [exemestane or fulvestrant]) as measured by the progression free survival (PFS) hazard ratio. This estimate will be precise enough to provide guidance for further development of AMG 479.for use in the planning of a phase 3 study in this patient population. Additionally, this study will provide qualitative estimates of PFS for treatment arms A and B.

Secondary Objectives: To investigate the effect of AMG 479 compared with placebo when administered in combination with exemestane or fulvestrant on:

- the safety and tolerability
- the impact to patient reported outcomes (PROs)
- the pharmacokinetics (PK) of AMG 479
- additional efficacy measures including clinical benefit rate, objective response rate, duration of response, time to progression (TTP), time-to-response, time-to-treatment failure, and survival time

Exploratory Objectives: To assess the potential effect of co-administration of AMG 479 and endocrine therapy (exemestane or fulvestrant) on the PK of the endocrine therapy (exemestane or fulvestrant).

To investigate the effect of AMG 479 compared with placebo when administered in combination with exemestane or fulvestrant on biomarkers using biochemical analysis of blood and tumor samples, including the correlation between biomarker measurements at baseline and/or in response to treatment outcomes.

To investigate the effect of genetic variation in drug metabolism genes, breast cancer genes, and drug target genes on treatment outcomes (this part of the study is optional for subjects).

Hypothesis: This study will provide an estimate of the relative efficacy of AMG 479 in combination with endocrine therapy (exemestane or fulvestrant) versus AMG 479 placebo in combination with endocrine therapy (exemestane or fulvestrant) as measured by the PFS hazard ratio. Additionally, this study will provide the estimate of PFS for each treatment arm.

Study Design: This is a randomized, double-blind, placebo-controlled, phase 2 study. Subjects will include postmenopausal women with confirmed hormone receptor (HR)-positive, locally advanced or metastatic breast cancer, who have disease progression during or within 12 months after completing prior adjuvant endocrine therapy or during the first prior endocrine therapy for metastatic disease.

Based on investigator discretion, subjects will be prescribed an endocrine therapy of either exemestane or fulvestrant to be administered throughout the study. The study plans to randomize 150 subjects in a 2:1 ratio to Arm A: AMG 479 in combination with endocrine therapy (exemestane or fulvestrant) or Arm B: placebo in combination with endocrine therapy (exemestane or fulvestrant).

At least 45 of the 150 subjects randomized will be required to be prescribed to each endocrine therapy (exemestane and fulvestrant).

Study treatment with AMG 479 or placebo and endocrine therapy (exemestane or fulvestrant) will continue until disease progression, unacceptable toxicity, consent withdrawal, investigator discretion, initiation of a new anticancer treatment, or death.

Subjects randomized to placebo in combination with endocrine therapy (Arm B) may have the opportunity to continue receiving study treatment as open-label AMG 479 in combination with the endocrine therapy originally prescribed ('roll over treatment') upon disease progression.

In order to safeguard the interest of the study subjects and maintain the study integrity, Amgen will form an unblinded data review team (DRT) that is external to the study team involved in the daily conduct of the study, but internal to Amgen to review safety data and efficacy analysis results.

Endpoints:

Primary: Progression free survival (PFS), as measured by Response Evaluation Criteria in Solid Tumors criteria (modified RECIST) per local review

Secondary:

- Clinical benefit (complete response, or partial response, or stable disease for ≥ 24 weeks as measured by modified RECIST per local review), objective response rate (complete and partial response as measured by modified RECIST per local review), duration of response, TTP, time-to-response, time-to-treatment failure, and survival
- Incidence of adverse events, abnormal laboratory values, and anti-AMG 479 antibody formation
- PK parameters of AMG 479
- Breast cancer related symptoms, health related quality of life, and skin toxicity burden

Exploratory: Objective response by tumor mutation status, biochemical concentrations and abundance of drug targets in tumor tissue and blood samples, genetic variations in drug metabolism genes and target genes (optional, separate informed consent required).

Sample Size: The study plans to randomize 150 subjects in a 2:1 ratio to Arm A: AMG 479 in combination with endocrine therapy (exemestane or fulvestrant) or Arm B: placebo in combination with endocrine therapy (exemestane or fulvestrant).

Key Subject Eligibility Criteria:

Inclusion

- Histologically or cytologically confirmed carcinoma of the breast with locally advanced or metastatic disease not amenable to surgery or radiation with curative intent (based on medical history review)
- Confirmation of HR (estrogen and/or progesterone receptor) positive disease using institutional standards for analysis of the primary tumor tissue or tissue obtained thereafter (based on medical history review)
- Amenable to receive endocrine therapy as per investigator discretion
- Disease progression while receiving prior endocrine therapy for locally advanced or metastatic breast cancer or recurrence while receiving prior endocrine therapy as adjuvant treatment or within 12 months of treatment discontinuation.
- Measurable or non-measurable disease, as defined by the modified RECIST criteria
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Postmenopausal woman (as defined by the protocol) ≥ 18 years old

- Adequate renal and hepatic function
- Adequate glycemic function, for subjects with known diabetes (Type 1 or 2)

Exclusion

- HR-unknown, or -negative disease (based on medical history review)
- Not amenable to receive endocrine therapy, including but not limited to, inflammatory breast cancer, rapidly progressing disease, or symptomatic visceral disease
- Central nervous system metastases, unless previously treated by either radiation therapy and/or surgical resection, who are clinically stable off corticosteroids before randomization
- More than 1 prior endocrine regimen for metastatic breast cancer, or locally advanced breast cancer. There are no restrictions for their administration in the neoadjuvant or adjuvant settings, except subjects should not have previously been treated with the endocrine therapy planned for use in this study
- More than 1 prior regimen including immunotherapy (eg, vaccines), antibody therapy (eg, trastuzumab, bevacizumab), small-molecule therapy (eg, lapatinib) for metastatic breast cancer, or locally advanced breast cancer, although there are no restrictions for their administration in the neoadjuvant or adjuvant settings
- More than 1 prior regimen including chemotherapy for metastatic breast cancer, or locally advanced breast cancer, although there are no restrictions for their administration in the neoadjuvant or adjuvant settings
- Administration of prior endocrine anticancer therapies within 1 week of randomization
- Administration of other prior anticancer therapies within 2 weeks of randomization

Key Subject Inclusion Criteria for Roll Over Treatment:

- Plan to continue study treatment as roll over treatment with open-label AMG 479 and the endocrine therapy prescribed at screening, if deemed to have been randomized to Arm B (placebo in combination with endocrine therapy [either exemestane or fulvestrant])
- Disease progression (according to local review using modified RECIST criteria) while receiving blinded study treatment
- Able to receive first dose of open-label AMG 479 within 4 weeks of disease progression
- Amenable to continue receiving endocrine therapy prescribed at screening, as per investigator discretion
- ECOG performance status of 0 or 1
- Adequate renal and hepatic function
- Adequate glycemic function, for subjects with known diabetes (Type 1 or 2)

Study Treatment Dosage and Administration: The AMG 479 dose to be used in the study is 12 mg/kg IV every 2 weeks. Based on investigator discretion, subjects will be prescribed an endocrine therapy of either exemestane (25 mg tablets once a day [QD] by mouth [PO]) or fulvestrant (loading dose [500 mg intramuscular (IM) on study day 1, then 250 mg IM on study day 15] then 250 mg IM on study day 29 and every 28 days thereafter) to be administered throughout the study. **AMG 479 or placebo will be administered by IV infusion through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with a 0.2- or 0.22-micron pore size in-line filter infusion set-up.**

Procedures: Informed consent, radiological assessments including bone scan and CT or MRI scans, clinical evaluations, hematology, coagulation factors, chemistry, HgbA1c, urine analysis, AMG 479, PK, biomarker and tumor tissue collection, concomitant medication collection, adverse event collection, and completion of PRO questionnaires.

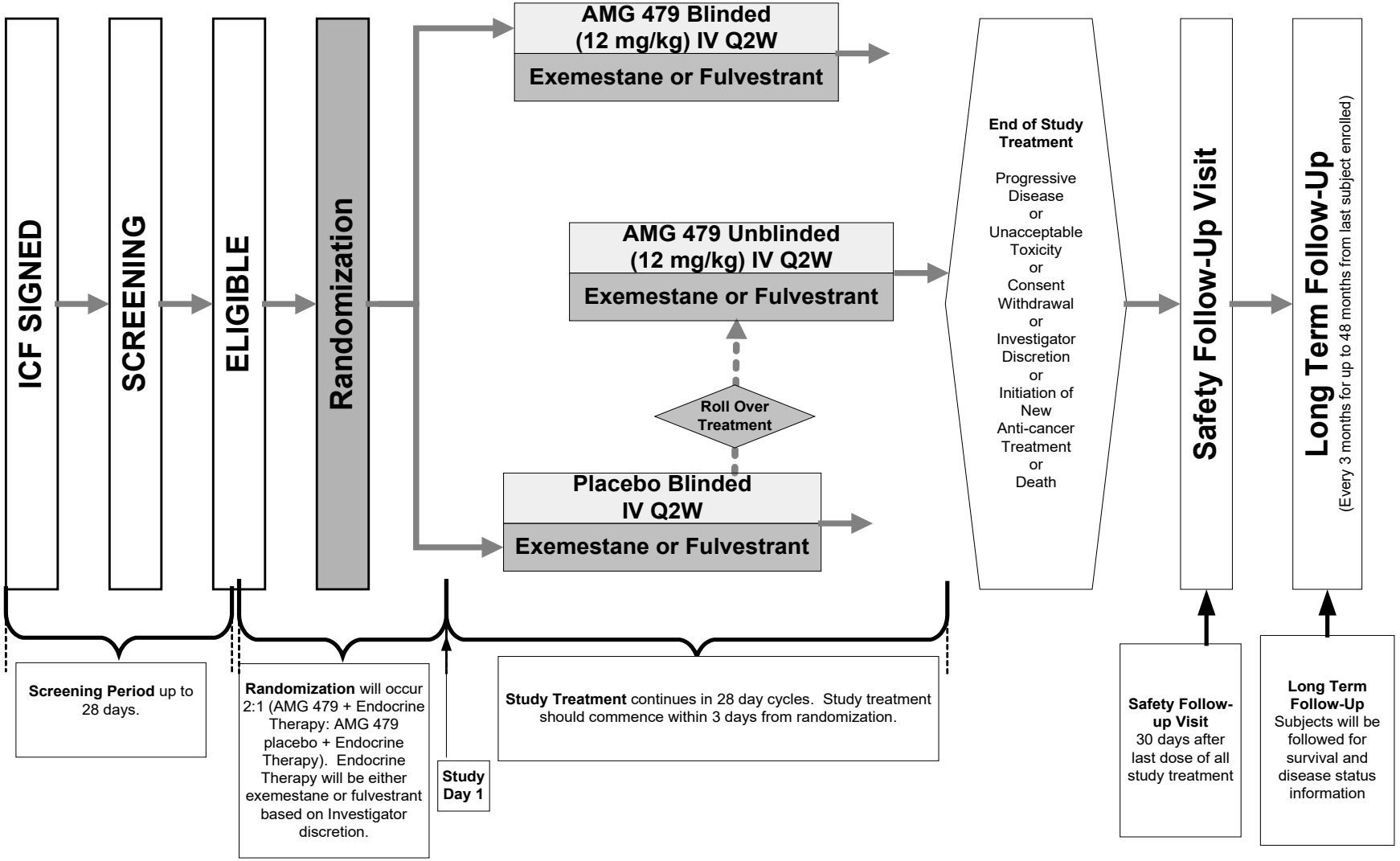
Statistical Considerations: The sample size of 150 subjects randomized in a 2:1 ratio for test versus control (Test: AMG 479 + fulvestrant or exemestane; Control: placebo + fulvestrant or exemestane) is intended to generate treatment effect estimates that may aid in the design of a potential phase 3 program for AMG 479. The desired increase in the median PFS, for subjects that received AMG 479 in combination with endocrine therapy that is believed to be clinically meaningful is 2 months (with a minimum increase of 1.5 months). Using a median PFS of 4 months for the treatment of placebo in combination with endocrine therapy (exemestane or fulvestrant), a 2 month absolute increase (50% relative increase) in the median PFS translates into a hazard ratio of 0.667 [test(n = 100)/control(n = 50)] and a 1.5 month absolute increase (37.5% relative increase) in the median PFS translates into a hazard ratio of 0.727.

Interim analyses of safety data will occur at the time 12 and 30 subjects have completed treatment administration for 2 months to assess safety and tolerability of the combination of AMG 479 or placebo with endocrine therapy (exemestane or fulvestrant). The DRT, will review cumulative safety data and make recommendations regarding study conduct. An interim analysis of efficacy and safety data is planned at the time 75 PFS events have occurred. This is estimated to occur approximately one month after the last subject is randomized. Summary statistics and Kaplan-Meier (K-M) plots of PFS by treatment arm, 80% confidence intervals for the estimated hazard ratio and the K-M estimated proportion of subjects without a PFS event at 6 months post-randomization will be generated. The stratified Cox model will be used to estimate the hazard ratio with respect to PFS (using the stratification factors) and to produce an 80% confidence interval for the hazard ratio.

All primary and secondary efficacy analyses will be conducted on the full analysis set. Subjects will be included in the analysis according to their randomized treatment assignment. The primary efficacy analysis will be performed when approximately 120 PFS events have been observed, where progression is based on local review. This is estimated to occur approximately 23 months after the first subject is randomized. At the time of the primary efficacy analysis, summaries will be provided for each safety, efficacy and PRO endpoint. The primary analysis of PFS will use the same methods utilized for the interim analysis of PFS.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema



Appendix A. Schedule of Assessments

	Screen	Study Treatment																	Safety FU[o]	Long-term FU[p]
Cycle		1			2		3		4		5		6		7		8		Assess for Roll Over[n]	
Cycle Days	-28	1	2	15	1	15	1	15	1	15	1	15	1	15	1	15	1	15		
Study Week	-4	1		3	5	7	9	11	13	15	17	19	21	23	25	27	29	31		
ENDOCRINE TREATMENT ADMINISTRATION[a]																				
Exemestane		←																→	X	
Fulvestrant		X		X	X		X		X		X		X		X		Q4W		X	
INVESTIGATIONAL PRODUCT ADMINISTRATION																				
AMG 479 or Placebo		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W		
GENERAL AND SAFETY ASSESSMENTS																				
Informed Consent	X																			
Review of Eligibility	X																		X	
Medical History/Clinical Evaluation[b]	X	X			X		X		X		X		X		X		Q4W		X	X	
Weight and Height[c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W	X	X	
Vitals[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W	X	X	
12-Lead ECG	X																			
Prior and Current Medication Collection	←																	→	X	X	
Adverse Events Collection	←																	→	X	X	
LABORATORY ASSESSMENTS																				
Blood Chemistry[e]	X	X[g]		X	X	X	X	X	X	X	X		X		X		Q4W		X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W	X	X	
Creatinine/Calculated Creatinine Clearance[f]	X																		X		
Coagulation	X	X[g]			X				X				X				Q8W		X	X	
TSH	X	X[g]			X				X				X				Q8W		X	X	
HgbA1C		X[g]			X				X				X				Q8W		X	X	
Endocrine Biomarker Collection		X		X	X		X				X				Q8W				X	X	
Other Biomarker Collection		X		X			X				X				Q8W				X	X	
Pharmacokinetics[h]		X		X	X		X				X				Q8W				X	X	
Anti-AMG 479 Antibody Assay		X			Q24W														X	X	
TUMOR RELATED ASSESSMENTS																				
Radiological Assessement[i]	X						X				X				Q8W						X
Bone Scan[j]	X								X								Q12W				X
Tumor Marker CA 15-3 or CA 27-29[k]	X						X				X				Q8W						
Tumor Sample[l]	X																				
PRO Assessments[m]		X			X		X		X						Q12W				X	X	
Survival Status																					X

CONTINUE ASSESSMENTS UNTIL PD, UNACCEPTABLE TOXICTY, CONSENT WITHDRAWL, PI DISCRETION OR DEATH

CONTINUE ASSESSMENTS UNTIL SUBSEQUENT PD, UNACCEPTABLE TOXICTY, CONSENT WITHDRAWL, PI DISCRETION OR DEATH

a Endocrine therapy (exemestane or fulvestrant) will be prescribed based on investigator discretion. Patients prescribed exemestane will have compliance reviewed and discussed with subject if needed at every clinic visit.

b Clinical evaluation, including physical exam performed, and ECOG status

c Height will only be collected at screening. Weight will be required pre-infusion to access the IVRS to obtain box assignment, quantity of vials and the volume of AMG 479 or placebo for infusion.

d Vitals, include blood pressure and respiration rate, pulse, and temperature.

e Blood chemistry will be analyzed at the local laboratory and will include: sodium, potassium, chloride, creatinine, CO_2, BUN, AST, ALT, alkaline phosphatase, and total bilirubin. Additionally fasting/non-fasting glucose will be assessed (fasting: screening, day 1 of cycles 1-4 then every second cycle, roll over treatment assessment [if applicable], and safety follow-up; non-fasting: day 15 of cycles 1-4, and day 1 cycle 5, then every second cycle)

f Either serum creatinine or calculated creatinine clearance (by Crockcroft-Gault formula)

g These laboratory assessments do not need to be performed on cycle 1 day 1 if they were performed during screening within 7 days of initiation of treatment

h Blood collections for PK analysis will occur for AMG 479 (pre- and post-AMG 479 infusion thru cycle 3), for exemestane (only for subjects prescribed exemestane; pre- and post-exemestane administration thru cycle 3), and for fulvestrant (only for subjects prescribed fulvestrant; pre-fulvestrant IM injection only thru cycle 3). No PK sample collection is needed for post-fulvestrant IM injection. Thereafter, blood collection for PK analysis of AMG 479, exemestane, and fulvestrant will only occur pre-dose every 2 cycles, starting cycle 5.

i Radiological assessments of the chest, abdomen and pelvis may occur by CT or MRI. The same technique used in screening must be used throughout the study. CT or MRI radiological assessments should occur on day 1 of cycle 3, then every 7 to 8 weeks thereafter.

j Subjects with a positive bone scan at screening will continue to have bone scans performed every 11 to 12 weeks thereafter while on study treatment. Subjects with a negative bone Scans will not be required to continue this procedure. Confirmatory bone images at baseline (CT with bone windows or MRI) at baseline and on during study treatment are required for positive areas on baseline bone scan as specified in Section 7.1.1.

k Subjects with a tumor marker CA 15-3 or CA 27-29 out of normal ranges at screening will continue to have this analyte analyzed while on study. The tumor marker selected at screening should remain the same throughout the study. Subjects with a tumor marker CA 15-3 or CA 27-29 within normal ranges at screening will not be required to continue this procedure.

l Tumor Sample (archived block, slides or fresh tissue collected for clinical care purposes) are to be obtained. A paraffin tumor block or fresh tissue from the most recent tumor tissue is preferred.

m PRO questionnaires should be completed before any other study procedures and before the patient is informed of their disease status

n Subjects will have a roll over visit, before initiating open-label AMG 479. This visit will allow assessment of roll over eligibility and will serve as the new baseline from which all changes will be compared. All subsequent visits and assessments will be performed according to the regular schedule of assessments continuing with the next per protocol visit after the last completed visit that occurred during blinded treatment.

o Safety FU- Safety follow-up visit is to be completed 30 to 37 days after last administration of protocol treatment

p All subjects who are alive at the time of discontinuation of protocol therapy will be followed approximately every 3 months for up to 48 months from the date of the last subject enrolled into the study to evaluate overall survival and disease status.