A PHASE 2 STUDY OF AMG 337 IN SUBJECTS WITH ADVANCED OR METASTATIC CLEAR CELL SARCOMA THAT CONTAINS THE *EWSR1-ATF1* GENE FUSION

Study Number:	**QUILT-3.031**
IND Sponsor:	NantPharma, LLC. 9920 Jefferson Blvd. Culver City, CA 90232
Funded by:	NantPharma, LLC. 9920 Jefferson Blvd. Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD-FACS Senior Vice President, Clinical Development NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Phone: +1-605-610-6391 Email: John.Lee@NantKwest.com

Protocol Version	**Date**
Version 1	12 April 2017

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the NantPharma, LLC. and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Site Investigator: <<Name>>

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantPharma, LLC.

Name of Investigational Product:
AMG 337

Name of Active Ingredient:
6-{(1R)-1-[8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)[1,2,4]triazolo[4,3-a]pyridin-3-yl]ethyl}-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one•hydrate (1:1)

Title of Study:
A phase 2 study of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion

Study Number:
QUILT-3.031

Study Phase:
Phase 2

Study Objectives:

- Primary Objective
  - To evaluate the efficacy of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion based on objective response rate (ORR) evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- Secondary Objectives
  - To evaluate the safety of AMG 337 based on grade 3 or 4 non-hematologic toxicity.
  - To determine progression-free survival (PFS) and overall survival (OS).
- Exploratory Objectives
  - To assess tumor molecular profiles (genomics, transcriptomics, and proteomics) and correlations with safety and efficacy outcomes.
  - To evaluate molecular changes in the MET pathway and potential compensatory pathways in pre- and post-treatment tumor biopsies.
  - To assess changes in circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA) during the study and correlations with efficacy outcomes.

Study Design:

This is a phase 2, single-arm, open-label study that will assess the efficacy of AMG 337 (based on ORR) in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion, as determined by fluorescent in situ hybridization (FISH) and confirmed by RNA sequencing (RNAseq). The study will be conducted using Simon's two-stage optimal design. The null hypothesis of Simon's two-stage design states that the ORR will be ≤ 40% (poor response) and will be tested against a one-sided alternative. In the first stage of Simon's two-stage design, 3 subjects will be enrolled. If ≤ 1 of these subjects has a confirmed response, the study will be terminated; otherwise, an additional 7 subjects will be enrolled in the second stage, for a total of 10 subjects. The null hypothesis, ORR ≤40%, will be rejected if ≥ 7 of 10 subjects has a response. This Simon's two-stage optimal design yields a one-sided type 1 error rate (α) of 4.6% with a power of 82% when the true response rate is 80% (optimal response).

Tumor biopsies and tumor molecular profiling will be performed as described in Section 6.1.2. Separate blood tubes will be collected every 2 weeks during routine blood draws to analyze blood for changes in ctDNA and ctRNA.

Toxicity stopping rules are in place to avoid excessive non-hematologic toxicities which are described in greater detail in the safety section of this protocol.

Primary Endpoints:

- Confirmed ORR (confirmed complete response [CR] or partial response [PR]) evaluated in accordance with RECIST Version 1.1.

Secondary Endpoints:

- Grade 3 or 4 non-hematologic toxicity.
- PFS evaluated in accordance with RECIST Version 1.1.
- OS.
- Duration of response, measured by RECIST Version 1.1.
- Disease control rate (confirmed CR, PR, or stable disease [SD]) lasting for at least 4 months.

Exploratory Endpoints:

- Tumor molecular profiles and correlations with safety and efficacy.
- Molecular changes in the MET pathway, and potential compensatory pathways in pre- and post-treatment tumor biopsies.
- Changes in ctDNA and ctRNA and correlations with efficacy outcomes.

Enrollment (planned):

This is a single-arm study using Simon's two-stage optimal design. The planned total enrollment is up to 10 subjects: 3 subjects enrolled in the first stage and an additional 7 subjects in the second stage.

Eligibility Criteria:

Inclusion Criteria:

1. Able to understand and provide a signed informed consent that fulfills the relevant IRB or IEC guidelines.
2. Able to attend required study visits and return for adequate follow-up, as required by this protocol.
3. Able to self-administer AMG 337 as a whole capsule by mouth every day.

4. Age ≥ 16 years.
5. Histologically confirmed, unresectable, locally advanced or metastatic tumors that contain the *EWSR1-ATF1* gene fusion, as determined by FISH and confirmed by RNAseq.
6. Have measurable disease evaluable in accordance with RECIST Version 1.1.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
8. Must have a recent FFPE tumor biopsy specimen that was obtained following the conclusion of the most recent anticancer treatment and be willing to release the specimen for tumor molecular profiling analysis. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period.
9. Must be willing to undergo a biopsy during the treatment period, if considered safe by the investigator.
10. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
11. Hematologic function, as follows:
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L.
    b. Platelet count ≥ 50×10^9/L.
    c. Hemoglobin > 8 g/dL.
    d. Prothrombin time (PT) or partial thromboplastin time (PTT) < 1.5 × upper limit of normal (ULN), except for subjects on anticoagulation therapy for venous thromboembolism.
12. Renal function, as follows:
    a. Calculated creatinine clearance > 30 mL/min.
13. Hepatic function, as follows:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × ULN and total bilirubin < 1.5 × ULN.
    b. Alkaline phosphatase (ALP) < 2 × ULN (≤ 5 × ULN if bone or liver metastases are present)
14. Agreement to practice effective contraception (both male and female subjects, if the risk of conception exists).

Exclusion Criteria:

1. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.
2. Inability to attend required study visits and return for adequate follow-up, as required for this protocol.
3. Known hypersensitivity to any component of the study medication(s).
4. Women who are nursing, pregnant, or planning to become pregnant during the duration of the study.

5. Current diagnosis or history of a second neoplasm, except the following:
    a. Adequately treated non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated with no evidence of disease for ≥ 2 years.
6. History of bleeding diathesis.
7. Uncontrolled hypertension (systolic > 160 mmHg and/or diastolic > 100 mmHg) or clinically significant cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months before study day 1; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
8. Baseline ECG Fridericia's formula QTcF > 470 ms.
9. Active infection requiring intravenous (IV) antibiotics within 2 weeks before study day 1.
10. Significant gastrointestinal disorder (eg, Crohn's disease, ulcerative colitis, extensive gastrointestinal resection) that in the opinion of the Investigator may influence drug absorption.
11. Positive result of screening test for human immunodeficiency virus (HIV).
12. Evidence of acute hepatitis B and C. Subjects with chronic hepatitis B or C are eligible if their condition is stable and, in the opinion of the investigator, would not pose a risk to subject safety.
13. Toxicities from prior anti-tumor therapy not resolved to CTCAE Version 4.03 grade 0 or 1.
    a. Grade 2 toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present or stable for > 4 weeks), such as stable grade 2 peripheral neuropathy or ifosfamide-related proteinuria, may be allowed if they are not otherwise described in the exclusion criteria.
14. Participation in this study or in an investigational study and/or procedure with any molecularly targeted agents reported to inhibit MET within 14 days before study day 1.
15. Anti-tumor therapy, including chemotherapy, antibody therapy, retinoid therapy, or other investigational therapy within 14 days before study day 1.
16. Therapeutic or palliative radiation therapy within 14 days before study day 1.
17. Major surgery within 28 days before study day 1.
18. Any comorbidity that in the opinion of the investigator may increase the risk of toxicity.
19. Concurrent or prior use of a strong CYP3A4 inhibitor within 14 days before study day 1, including the following: ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.
20. Concurrent or prior ingestion of grapefruit or grapefruit products, or other foods known to inhibit CYP3A4 within 7 days before study day 1.
21. Concurrent or prior use of strong CYP3A4 inducers within 28 days before study day 1, including the following: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, or the herbal supplement St. John's Wort.

Investigational Product, Dosage, and Mode of Administration:

Subjects will self-administer AMG 337 orally (PO) twice a day (BID, approximately every 12 hours) in a fasted state. Subjects shall refrain from food and liquid intake for 1 hour post-dose, except for water, medications, or liquids as recommended by the investigator (eg, 100 mg caffeine, in the form of a tablet or caffeine-containing beverage, to prevent headaches).

Dose levels of AMG 337 are as follows:

- Dose level 0: 150 mg BID (300 mg/day total)
- Dose level -1: 100 mg BID (200 mg/day total)

Subjects will start at dose level 0. Adjustments to the dose will be made based on grade 3 or 4 drug-related toxicities.

AMG 337 will be manufactured, packaged, and distributed by NantPharma, LLC. in accordance with Good Manufacturing Practice (GMP) standards. AMG 337 hydrate (freebase equivalent) is formulated as an immediate-release capsule in strengths of 50-mg and 100-mg of AMG 337. The 50-mg strength is presented as grey, opaque, size 3, hard, gelatin capsules, and the 100-mg strength is presented as white, opaque, size 1, hard, gelatin capsules. The formulation also contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

AMG 337 capsules will be supplied in High Density Polyethylene (HDPE) bottles closed with an aluminum induction heat seal and a child-resistant polypropylene closure containing 30 capsules per bottle and provided in strengths of 50 mg and 100 mg. No other Investigational Product shall be used or provided in this study.

Duration of Treatment: Subjects will self-administer AMG 337 PO BID. Subjects will be treated with AMG 337 until they experience progressive disease (PD), unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up: After the subject progresses, completes, or withdraws from the study, the subject will be followed approximately every 3 months for 24 months to collect follow-up information, including survival status and any current cancer treatment regimen. Beyond the initial 24 months, the subject will be contacted every 6 months for an additional 24 months.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety: Safety evaluations include assessments of AEs, SAEs, safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Efficacy: ORR and PFS will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and will be evaluated in accordance with RECIST Version 1.1. Imaging assessments will begin between day -28 and day -1. Restaging evaluations will occur at 8-week intervals for the first 16 weeks and at regular 3-month intervals thereafter until disease progression. OS will also be evaluated.

Exploratory Analyses:

Molecular Profiling and Analysis: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Plasma will be obtained from whole blood and a PCR-based assay will be used to detect and quantify DNA mutations and RNA expression in ctDNA and ctRNA.

MET Pathway Analysis: Molecular changes in the MET pathway will be evaluated in pre- and post-treatment tumor biopsies by genomic sequencing, RNA sequencing, and quantitative proteomics analysis.

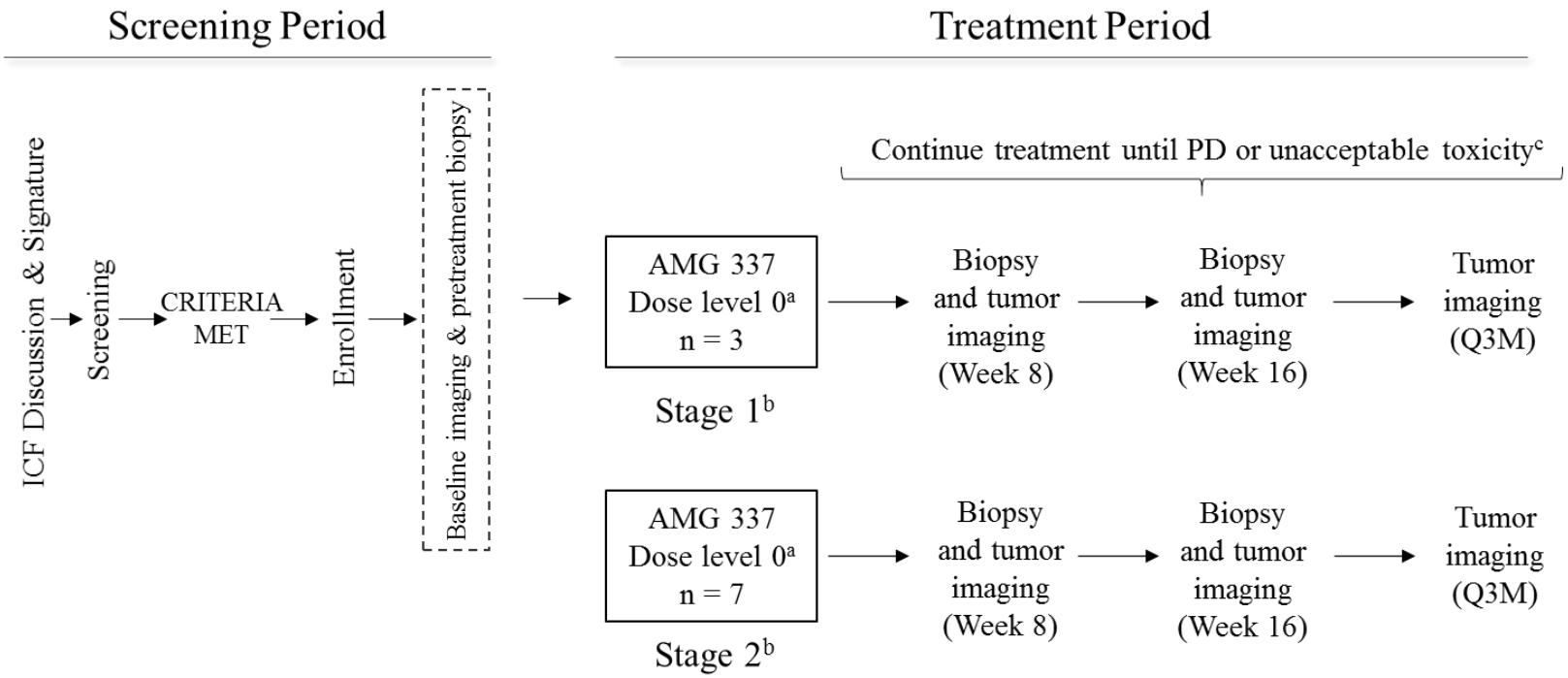
Statistical Methods:

The primary efficacy endpoint, ORR, will be evaluated in accordance with RECIST Version 1.1. The percentage of subjects who achieve a confirmed response (and 95% confidence interval [CI]) will be summarized. Disease control rate will be evaluated using the same methods as ORR. PFS, OS, and duration of response will be analyzed using Kaplan-Meier methods.

Overall safety will be assessed by descriptive statistics. AEs will be graded by CTCAE Version 4.03 and coded using Medical Dictionary for Regulatory Activities (MedDRA). Tabulated frequencies of overall treatment-emergent AEs, SAEs, and AEs causing treatment modifications will be presented. Clinically significant changes in laboratory tests, physical examinations, ECGs, and vital signs will be evaluated.

Correlations between the levels of specific biomarkers in ctDNA and ctRNA and efficacy outcomes will be explored.

Figure 1: Study Treatment Schema



[a]The starting dose (dose level 0) is 150 mg BID PO (300 mg/day total). Adjustments to the dose will be made based on grade 3 or 4 drug-related toxicities, with a planned dose level -1 of 100 mg BID PO (200 mg/day total).
[b]In the first stage of Simon's two-stage design, 3 subjects will be enrolled. If ≤ 1 of these subjects exhibits a confirmed response, the study will be terminated; otherwise, an additional 7 subjects will be enrolled in the second stage, for a total of 10 subjects.
[c]Subjects will be treated with AMG 337 until they experience PD or unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.
PD, progressive disease; Q3M, every 3 months.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	A phase 2 study of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion.
Study Number:	QUILT-3.031
Version Number:	1
Final Date:	12 April 2017

This clinical trial protocol was subject to critical review and has been approved by NantPharma, LLC. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 4-12-17

John H. Lee, MD-FACS
Senior Vice President, Clinical Development
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A PHASE 2 STUDY OF AMG 337 IN SUBJECTS WITH ADVANCED OR METASTATIC CLEAR CELL SARCOMA THAT CONTAINS THE *EWSR1-ATF1* GENE FUSION

Study Number:	**QUILT-3.031**
IND Sponsor:	NantPharma, LLC. 9920 Jefferson Blvd. Culver City, CA 90232
Funded by:	NantPharma, LLC. 9920 Jefferson Blvd. Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD-FACS Senior Vice President, Clinical Development NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Phone: +1-605-610-6391 Email: John.Lee@NantKwest.com

Protocol Version	**Date**
Version 1	12 April 2017
Version 2	7 December 2017

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the NantPharma, LLC. and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Site Investigator: <<Name>>

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantPharma, LLC.

Name of Investigational Product:
AMG 337

Name of Active Ingredient:
6-{(1R)-1-[8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)[1,2,4]triazolo[4,3-a]pyridin-3-yl]ethyl}-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one•hydrate (1:1)

Title of Study:
A phase 2 study of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion

Study Number:
QUILT-3.031

Study Phase:
Phase 2

Study Objectives:

- Primary Objective
  - To evaluate the efficacy of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion based on objective response rate (ORR) evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- Secondary Objectives
  - To evaluate the safety of AMG 337 based on grade 3 or 4 non-hematologic toxicity.
  - To determine progression-free survival (PFS), overall survival (OS), duration of response (DOR), and disease control rate (DCR).
- Exploratory Objectives
  - To assess tumor molecular profiles (genomics, transcriptomics, and proteomics) and correlations with subject outcomes.
  - To evaluate molecular changes in the MET pathway and potential compensatory pathways in pre- and post-treatment tumor biopsies.
  - To assess molecular changes in circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA) during the study and their correlations with subject outcomes.

Study Design:
This is a phase 2, single-arm, open-label study that will assess the efficacy of AMG 337 (based on ORR) in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion, as determined by fluorescent in situ hybridization (FISH) and confirmed by RNA sequencing (RNAseq). The study will be conducted using Simon's two-stage optimal design. The null hypothesis

of Simon's two-stage design states that the ORR will be ≤ 40% (poor response) and will be tested against a one-sided alternative. In the first stage of Simon's two-stage design, 3 subjects will be enrolled. If ≤ 1 of these subjects has a confirmed response, the study will be terminated; otherwise, an additional 7 subjects will be enrolled in the second stage, for a total of 10 subjects. The null hypothesis, ORR ≤ 40%, will be rejected if ≥ 7 of 10 subjects has a response. This Simon's two-stage optimal design yields a one-sided type 1 error rate (α) of 4.6% with a power of 82% when the true response rate is 80% (optimal response).

Tumor biopsies and exploratory tumor molecular profiling will be performed as described in Section 6.1.2 and Section 6.4.1, respectively. Separate blood tubes will be collected every 4 weeks for the first 12 weeks and every 8 weeks thereafter during routine blood draws for exploratory ctDNA/ctRNA analyses, as described in Section 6.4.3.

Toxicity stopping rules are in place to avoid excessive non-hematologic toxicities which are described in greater detail in the safety section of this protocol.

Primary Endpoints:

- Confirmed ORR (confirmed complete response [CR] or partial response [PR]) evaluated in accordance with RECIST Version 1.1.

Secondary Endpoints:

- Grade 3 or 4 non-hematologic toxicity.
- PFS evaluated in accordance with RECIST Version 1.1.
- OS.
- DOR, measured by RECIST Version 1.1.
- DCR (confirmed CR, PR, or stable disease [SD]) lasting for at least 4 months.

Exploratory Endpoints:

- Tumor molecular profiles and correlations with safety and efficacy.
- Molecular changes in the MET pathway, and potential compensatory pathways in pre- and post-treatment tumor biopsies.
- Molecular changes in ctDNA and ctRNA and correlations with subject outcomes.

Enrollment (planned):

This is a single-arm study using Simon's two-stage optimal design. The planned total enrollment is up to 10 subjects: 3 subjects enrolled in the first stage and an additional 7 subjects in the second stage.

Eligibility Criteria:

Inclusion Criteria:

1. Able to understand and provide a signed informed consent that fulfills the relevant IRB or IEC guidelines.
2. Able to attend required study visits and return for adequate follow-up, as required by this protocol.
3. Able to self-administer AMG 337 as a whole capsule by mouth every day.
4. Age ≥ 16 years.
5. Histologically confirmed, unresectable, locally advanced or metastatic tumors that contain the *EWSR1-ATF1* gene fusion, as determined by FISH and confirmed by RNAseq.

6. Have measurable disease evaluable in accordance with RECIST Version 1.1.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
8. Must have a recent FFPE tumor biopsy specimen that was obtained following the conclusion of the most recent anticancer treatment and be willing to release the specimen for *EWSR1-ATF1* gene fusion confirmation and for tumor molecular profiling analysis. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy specimen during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
9. Must be willing to undergo a biopsy during the treatment period, if considered safe by the investigator.
10. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
11. Hematologic function, as follows:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
    b. Platelet count $\geq 50 \times 10^9$/L.
    c. Hemoglobin > 8 g/dL.
    d. Prothrombin time (PT) or partial thromboplastin time (PTT) < 1.5 × upper limit of normal (ULN), except for subjects on anticoagulation therapy for venous thromboembolism.
12. Renal function, as follows:
    a. Calculated creatinine clearance > 30 mL/min.
13. Hepatic function, as follows:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × ULN and total bilirubin < 1.5 × ULN.
    b. Alkaline phosphatase (ALP) < 2 × ULN (≤ 5 × ULN if bone or liver metastases are present)
14. Agreement to practice effective contraception (both male and female subjects, if the risk of conception exists).

Exclusion Criteria:

1. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.
2. Inability to attend required study visits and return for adequate follow-up, as required for this protocol.
3. Known hypersensitivity to any component of the study medication(s).
4. Women who are nursing, pregnant, or planning to become pregnant during the duration of the study.
5. Current diagnosis or history of a second neoplasm, except the following:
    a. Adequately treated non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated with no evidence of disease for ≥ 2 years.

6. History of bleeding diathesis.
7. Uncontrolled hypertension (systolic > 160 mmHg and/or diastolic > 100 mmHg) or clinically significant cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months before study day 1; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
8. Baseline ECG Fridericia's formula QTcF > 470 ms.
9. Active infection requiring intravenous (IV) antibiotics within 2 weeks before study day 1.
10. Significant gastrointestinal disorder (eg, Crohn's disease, ulcerative colitis, extensive gastrointestinal resection) that in the opinion of the Investigator may influence drug absorption.
11. Positive result of screening test for human immunodeficiency virus (HIV).
12. Evidence of acute hepatitis B and C. Subjects with chronic hepatitis B or C are eligible if their condition is stable and, in the opinion of the investigator, would not pose a risk to subject safety.
13. Toxicities from prior anti-tumor therapy not resolved to CTCAE Version 4.03 grade 0 or 1.
    a. Grade 2 toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present or stable for > 4 weeks), such as stable grade 2 peripheral neuropathy or ifosfamide-related proteinuria, may be allowed if they are not otherwise described in the exclusion criteria.
14. Participation in this study or in an investigational study and/or procedure with any molecularly targeted agents reported to inhibit MET within 14 days before study day 1.
15. Anti-tumor therapy, including chemotherapy, antibody therapy, retinoid therapy, or other investigational therapy within 14 days before study day 1.
16. Therapeutic or palliative radiation therapy within 14 days before study day 1.
17. Major surgery within 28 days before study day 1.
18. Any comorbidity that in the opinion of the investigator may increase the risk of toxicity.
19. Concurrent or prior use of a strong CYP3A4 inhibitor within 14 days before study day 1, including the following: ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.
20. Concurrent or prior ingestion of grapefruit or grapefruit products, or other foods known to inhibit CYP3A4 within 7 days before study day 1.
21. Concurrent or prior use of strong CYP3A4 inducers within 28 days before study day 1, including the following: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, or the herbal supplement St. John's Wort.

Investigational Product, Dosage, and Mode of Administration:

Subjects will self-administer AMG 337 orally (PO) twice a day (BID, approximately every 12 hours) in a fasted state. Subjects shall refrain from food and liquid intake for 1 hour post-dose, except for water, medications, or liquids as recommended by the investigator (eg, 100 mg caffeine, in the form of a tablet or caffeine-containing beverage, to prevent headaches).

Dose levels of AMG 337 are as follows:

- Dose level 0: 150 mg BID (300 mg/day total)
- Dose level -1: 100 mg BID (200 mg/day total)

Subjects will start at dose level 0. Adjustments to the dose will be made based on grade 3 or 4 drug-related toxicities.

AMG 337 will be manufactured, packaged, and distributed by NantPharma, LLC. in accordance with Good Manufacturing Practice (GMP) standards. AMG 337 hydrate (freebase equivalent) is formulated as an immediate-release capsule in strengths of 50-mg and 100-mg of AMG 337. The 50-mg strength is presented as grey, opaque, size 3, hard, gelatin capsules, and the 100-mg strength is presented as white, opaque, size 1, hard, gelatin capsules. The formulation also contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

AMG 337 capsules will be supplied in High Density Polyethylene (HDPE) bottles closed with an aluminum induction heat seal and a child-resistant polypropylene closure containing 30 capsules per bottle and provided in strengths of 50 mg and 100 mg. No other Investigational Product shall be used or provided in this study.

Duration of Treatment: Subjects will self-administer AMG 337 PO BID. Subjects will be treated with AMG 337 until they experience progressive disease (PD), unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up: After the subject progresses, completes, or withdraws from the study, the subject will be followed approximately every 3 months for 24 months to collect follow-up information, including survival status and any current cancer treatment regimen. Beyond the initial 24 months, the subject will be contacted every 6 months for an additional 24 months.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety: Safety evaluations include assessments of AEs, SAEs, safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Efficacy: ORR and PFS will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and will be evaluated in accordance with RECIST Version 1.1. Imaging assessments will begin between day -28 and day -1. Restaging evaluations will occur at 8-week intervals for the first 16 weeks and at regular 3-month intervals thereafter until disease progression. OS will also be evaluated.

Exploratory Analyses:

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor -specific genomic variances that may contribute to disease progression and/or response to treatment. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the absolute amounts of specific proteins, to confirm expression of genes that are correlative of disease progression and/or response, and to determine cutoff values for response.

MET Pathway Analysis: Molecular changes in the MET pathway will be evaluated in pre- and post-treatment tumor biopsies by genomic sequencing, RNA sequencing, and quantitative proteomics analysis.

ctDNA/ctRNA Analysis: ctDNA and ctRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and analyzed for correlations with subject outcomes.

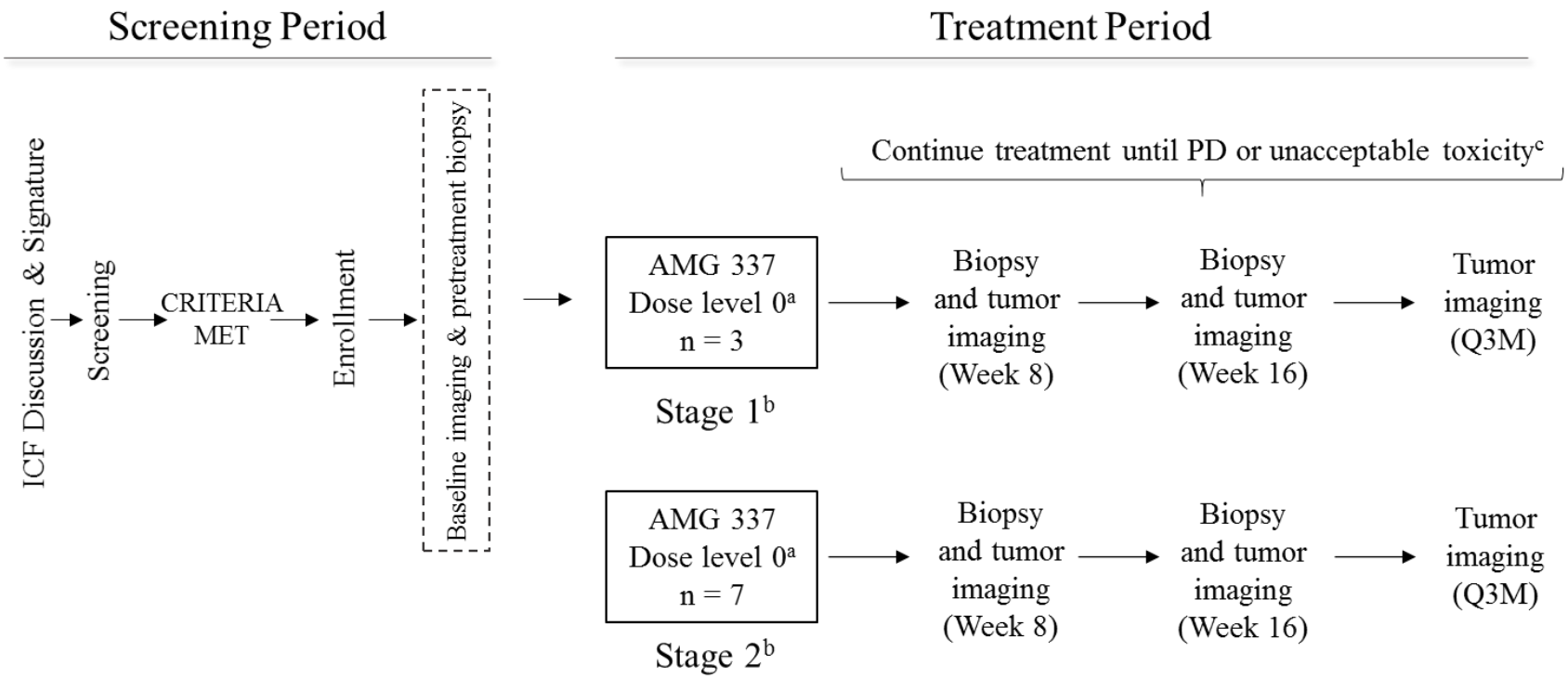
Statistical Methods:

The primary efficacy endpoint, ORR, will be evaluated in accordance with RECIST Version 1.1. The percentage of subjects who achieve a confirmed response (and 95% confidence interval [CI]) will be summarized. Disease control rate will be evaluated using the same methods as ORR. PFS, OS, and duration of response will be analyzed using Kaplan-Meier methods.

Overall safety will be assessed by descriptive statistics. AEs will be graded by CTCAE Version 4.03 and coded using Medical Dictionary for Regulatory Activities (MedDRA). Tabulated frequencies of overall treatment-emergent AEs, SAEs, and AEs causing treatment modifications will be presented. Clinically significant changes in laboratory tests, physical examinations, ECGs, and vital signs will be evaluated.

Correlations between the levels of specific biomarkers in ctDNA and ctRNA and subject outcomes will be explored.

Figure 1: Study Treatment Schema



[a]The starting dose (dose level 0) is 150 mg BID PO (300 mg/day total). Adjustments to the dose will be made based on grade 3 or 4 drug-related toxicities, with a planned dose level -1 of 100 mg BID PO (200 mg/day total).
[b]In the first stage of Simon's two-stage design, 3 subjects will be enrolled. If ≤ 1 of these subjects exhibits a confirmed response, the study will be terminated; otherwise, an additional 7 subjects will be enrolled in the second stage, for a total of 10 subjects.
[c]Subjects will be treated with AMG 337 until they experience PD or unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.
PD, progressive disease; Q3M, every 3 months.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	A phase 2 study of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion.
Study Number:	QUILT-3.031
Version Number:	2
Final Date:	7 December 2017

This clinical trial protocol was subject to critical review and has been approved by NantPharma, LLC. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 12-11-17

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A PHASE 2 STUDY OF AMG 337 IN SUBJECTS WITH ADVANCED OR METASTATIC CLEAR CELL SARCOMA THAT CONTAINS THE *EWSR1-ATF1* GENE FUSION

Study Number:	**QUILT-3.031**
IND Sponsor:	NantPharma, LLC. 9920 Jefferson Blvd. Culver City, CA 90232
Funded by:	NantPharma, LLC. 9920 Jefferson Blvd. Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD-FACS Chief Medical Officer ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Phone: +1-605-610-6391 Email: John.Lee@ImmunityBio.com

Protocol Version	**Date**
Version 1	12 April 2017
Version 2	7 December 2017
Version 3	07 November 2019

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6 R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the NantPharma, LLC. and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Site Investigator: <<Name>>

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantPharma, LLC.

Name of Investigational Product:
AMG 337

Name of Active Ingredient:
6-{(1R)-1-[8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)[1,2,4]triazolo[4,3-a]pyridin-3-yl]ethyl}-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one•hydrate (1:1)

Title of Study:
A phase 2 study of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion

Study Number:
QUILT-3.031

Study Phase:
Phase 2

Study Objectives:

- Primary Objective
  - To evaluate the efficacy of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion based on objective response rate (ORR) evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 by Blinded Independent Central Review (BICR).
- Secondary Objectives
  - To evaluate the safety of AMG 337 based on grade 3 or 4 non-hematologic toxicity.
  - To determine progression-free survival (PFS), overall survival (OS), duration of response (DOR), and disease control rate (DCR).
- Exploratory Objectives
  - To assess tumor molecular profiles (genomics and transcriptomics) and correlations with subject outcomes.
  - To evaluate molecular changes in the MET pathway and potential compensatory pathways in pre- and post-treatment tumor biopsies.

Study Design:
This is a phase 2, single-arm, open-label study that will assess the efficacy of AMG 337 (based on confirmed ORR) in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion, as determined by fluorescent in situ hybridization (FISH) or other diagnostic methods and confirmed by RNA sequencing (RNAseq).

Tumor biopsies and exploratory tumor molecular profiling will be performed as described in Section 6.1.2 and Section 6.4.1, respectively.

Toxicity stopping rules are in place to avoid excessive non-hematologic toxicities which are described in greater detail in the safety section of this protocol.

Primary Endpoints:

- Confirmed ORR (confirmed complete response [CR] or partial response [PR]) evaluated in accordance with RECIST Version 1.1 by BICR.

Secondary Endpoints:

- Grade 3 or 4 non-hematologic toxicity.
- PFS evaluated in accordance with RECIST Version 1.1 by BICR.
- OS.
- DOR, measured by RECIST Version 1.1 by BICR.
- DCR (confirmed CR, PR, or stable disease [SD]) lasting for at least 4 months by BICR.

Exploratory Endpoints:

- Tumor molecular profiles and correlations with safety and efficacy.
- Molecular changes in the MET pathway, and potential compensatory pathways in pre- and post-treatment tumor biopsies.

Enrollment (planned):

This is a single-arm study. The planned total enrollment is up to 37 subjects.

Eligibility Criteria:

Inclusion Criteria:

1. Able to understand and provide a signed informed consent that fulfills the relevant IRB or IEC guidelines.
2. Able to attend required study visits and return for adequate follow-up, as required by this protocol.
3. Able to self-administer AMG 337 as a whole capsule by mouth every day.
4. Age ≥ 16 years.
5. Histologically confirmed, unresectable, locally advanced or metastatic tumors that contain the *EWSR1-ATF1* gene fusion, as determined by FISH or other diagnostic methods and confirmed by RNAseq.
6. Have measurable disease evaluable in accordance with RECIST Version 1.1.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
8. Must have a recent FFPE tumor biopsy specimen that was obtained following the conclusion of the most recent anticancer treatment and be willing to release the specimen for *EWSR1-ATF1* gene fusion confirmation and for tumor molecular profiling analysis. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy specimen during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.

9. Must be willing to undergo a biopsy during the treatment period, if considered safe by the investigator.
10. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
11. Hematologic function, as follows:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
    b. Platelet count $\geq 50 \times 10^9$/L.
    c. Hemoglobin > 8 g/dL.
    d. Prothrombin time (PT) or partial thromboplastin time (PTT) < 1.5 × upper limit of normal (ULN), except for subjects on anticoagulation therapy for venous thromboembolism.
12. Renal function, as follows:
    a. Calculated creatinine clearance > 30 mL/min.
13. Hepatic function, as follows:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × ULN and total bilirubin < 1.5 × ULN.
    b. Alkaline phosphatase (ALP) < 2 × ULN (≤ 5 × ULN if bone or liver metastases are present)
14. Agreement to practice effective contraception (both male and female subjects, if the risk of conception exists).

Exclusion Criteria:

1. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.
2. Inability to attend required study visits and return for adequate follow-up, as required for this protocol.
3. Known hypersensitivity to any component of the study medication(s).
4. Women who are nursing, pregnant, or planning to become pregnant during the duration of the study.
5. Current diagnosis or history of a second neoplasm, except the following:
    a. Adequately treated non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated with no evidence of disease for ≥ 2 years.
6. History of bleeding diathesis.
7. Uncontrolled hypertension (systolic > 160 mmHg and/or diastolic > 100 mmHg) or clinically significant cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months before study day 1; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
8. Baseline ECG Fridericia's formula QTcF > 470 ms.
9. Active infection requiring intravenous (IV) antibiotics within 2 weeks before study day 1.

10. Significant gastrointestinal disorder (eg, Crohn's disease, ulcerative colitis, extensive gastrointestinal resection) that in the opinion of the Investigator may influence drug absorption.
11. Positive result of screening test for human immunodeficiency virus (HIV).
12. Evidence of acute hepatitis B and C. Subjects with chronic hepatitis B or C are eligible if their condition is stable and, in the opinion of the investigator, would not pose a risk to subject safety.
13. Toxicities from prior anti-tumor therapy not resolved to CTCAE Version 4.03 grade 0 or 1.
    a. Grade 2 toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present or stable for > 4 weeks), such as stable grade 2 peripheral neuropathy or ifosfamide-related proteinuria, may be allowed if they are not otherwise described in the exclusion criteria.
14. Participation in this study or in an investigational study and/or procedure with any molecularly targeted agents reported to inhibit MET within 14 days before study day 1.
15. Anti-tumor therapy, including chemotherapy, antibody therapy, retinoid therapy, or other investigational therapy within 14 days before study day 1.
16. Therapeutic or palliative radiation therapy within 14 days before study day 1.
17. Major surgery within 28 days before study day 1.
18. Any comorbidity that in the opinion of the investigator may increase the risk of toxicity.
19. Concurrent or prior use of a strong CYP3A4 inhibitor within 14 days before study day 1, including the following: ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.
20. Concurrent or prior ingestion of grapefruit or grapefruit products, or other foods known to inhibit CYP3A4 within 7 days before study day 1.
21. Concurrent or prior use of strong CYP3A4 inducers within 28 days before study day 1, including the following: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, or the herbal supplement St. John's Wort.

Investigational Product, Dosage, and Mode of Administration:

Subjects will self-administer AMG 337 orally (PO) twice a day (BID, approximately every 12 hours) in a fasted state. Subjects shall refrain from food and liquid intake for 1 hour post-dose, except for water, medications, or liquids as recommended by the investigator (eg, 100 mg caffeine, in the form of a tablet or caffeine-containing beverage, to prevent headaches).

Dose levels of AMG 337 are as follows:

- Dose level 0: 150 mg BID (300 mg/day total)
- Dose level -1: 100 mg BID (200 mg/day total)

Subjects will start at dose level 0. Adjustments to the dose will be made based on grade 3 or 4 drug-related toxicities.

AMG 337 will be manufactured, packaged, and distributed by NantPharma, LLC. in accordance with Good Manufacturing Practice (GMP) standards. AMG 337 hydrate (freebase equivalent) is formulated as an immediate-release capsule in strengths of 50-mg and 100-mg of AMG 337. The 50-mg strength is presented as grey, opaque, size 3, hard, gelatin capsules, and the 100-mg strength is presented as

white, opaque, size 1, hard, gelatin capsules. The formulation also contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

AMG 337 capsules will be supplied in High Density Polyethylene (HDPE) bottles closed with an aluminum induction heat seal and a child-resistant polypropylene closure containing 30 capsules per bottle and provided in strengths of 50 mg and 100 mg. No other Investigational Product shall be used or provided in this study.

Duration of Treatment: Subjects will self-administer AMG 337 PO BID. Subjects will be treated with AMG 337 until they experience progressive disease (PD), unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up: After the subject progresses, completes, or withdraws from the study, the subject will be followed approximately every 3 months for 24 months to collect follow-up information, including survival status and any current cancer treatment regimen. Beyond the initial 24 months, the subject will be contacted every 6 months for an additional 24 months.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety: Safety evaluations include assessments of AEs, SAEs, safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Efficacy: Tumor response will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and will be evaluated in accordance with RECIST Version 1.1. Imaging assessments will begin between day -28 and day -1. Restaging evaluations will occur at 8-week intervals for the first 16 weeks and at regular 3-month intervals thereafter until disease progression. OS will also be evaluated.

Exploratory Analyses:

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor -specific genomic variances that may contribute to disease progression and/or response to treatment. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations.

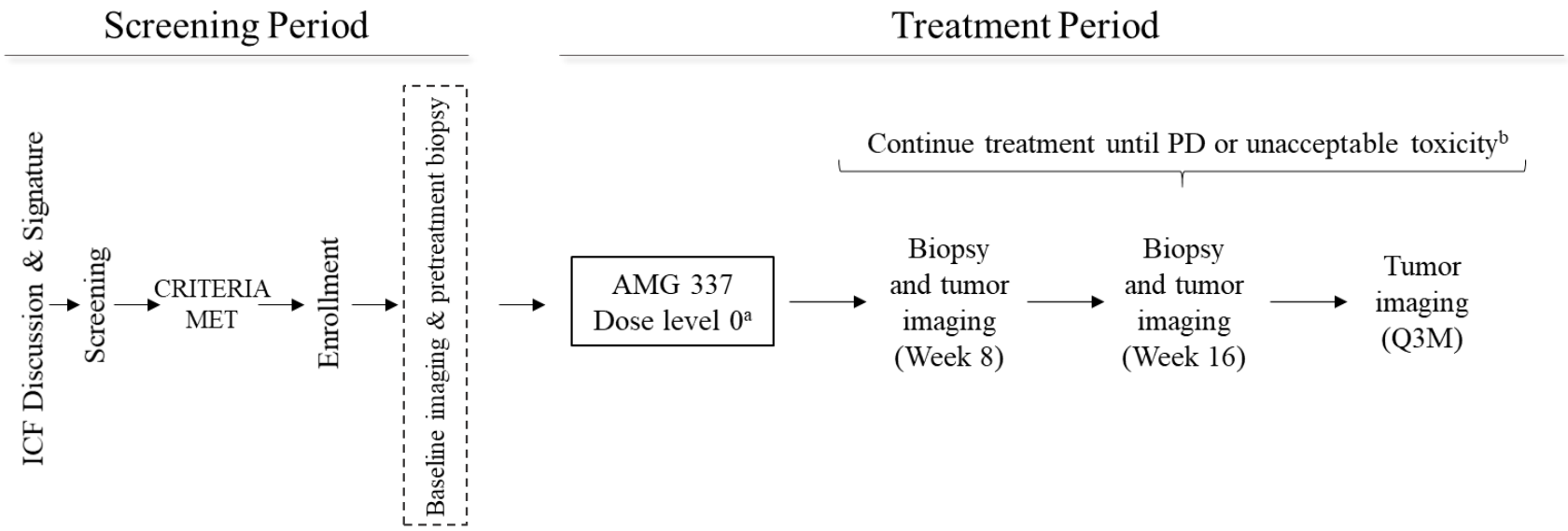
MET Pathway Analysis: Molecular changes in the MET pathway will be evaluated in pre- and post-treatment tumor biopsies by genomic sequencing, and RNA sequencing.

Statistical Methods:

The primary efficacy endpoint, confirmed ORR, will be evaluated in accordance with RECIST Version 1.1 by BICR. The ORR and its two-sided 95% exact confidence interval (CI) will be summarized. The exact CI will be calculated using the Clopper-Pearson method. For the primary endpoint to be successful, the lower limit of the exact CI should be > 10%. DCR will be evaluated using the same methods as ORR. PFS, OS, and DOR will be analyzed using Kaplan-Meier methods.

Overall safety will be assessed by descriptive statistics. AEs will be graded by CTCAE Version 4.03 and coded using Medical Dictionary for Regulatory Activities (MedDRA). Tabulated frequencies of overall treatment-emergent AEs, SAEs, and AEs causing treatment modifications will be presented. Clinically significant changes in laboratory tests, physical examinations, ECGs, and vital signs will be evaluated.

Figure 1: Study Treatment Schema



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[b]Subjects will be treated with AMG 337 until they experience PD or unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment.
Abbreviations: PD, progressive disease; Q3M, every 3 months.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	A phase 2 study of AMG 337 in subjects with advanced or metastatic clear cell sarcoma that contains the *EWSR1-ATF1* gene fusion.
Study Number:	QUILT-3.031
Version Number:	3
Final Date:	07 November 2019

This clinical trial protocol was subject to critical review and has been approved by NantPharma, LLC. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: Nov-7 2019

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