# The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed Hormone Sensitive Prostate Cancer

**Protocol #115523**
**(Aragon Protocol ARN-509-002)**

**Study Drug: ARN-509**

**Version Number: 15.0**
**Version Date: 01 February 2019**

**IND #: 104,676 (Held by Aragon Pharmaceuticals, Inc.*)**

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**Revision History**

| | |
|---|---|
| Version 15.0 | 02-01-19 |
| Version 14.0 | 08-16-16 |
| Version 13.0 | 08-15-16 |
| Version 12.0 | 06-15-16 |
| Version 11.0 | 06-13-16 |
| Version 10.0 | 06-01-16 |
| Version 9.0 | 09-30-15 |
| Version 8.0 | 09-28-15 |
| Version 7.0 | 09-12-14 |
| Version 6.0 | 06-03-14 |
| Version 5.0 | 01-31-13 |
| Version 4.0 | 07-06-12 |
| Version 3.0 | 04-13-12 |
| Version 2.0 | 01-11-12 |
| Version 1.0 | 11-20-11 |

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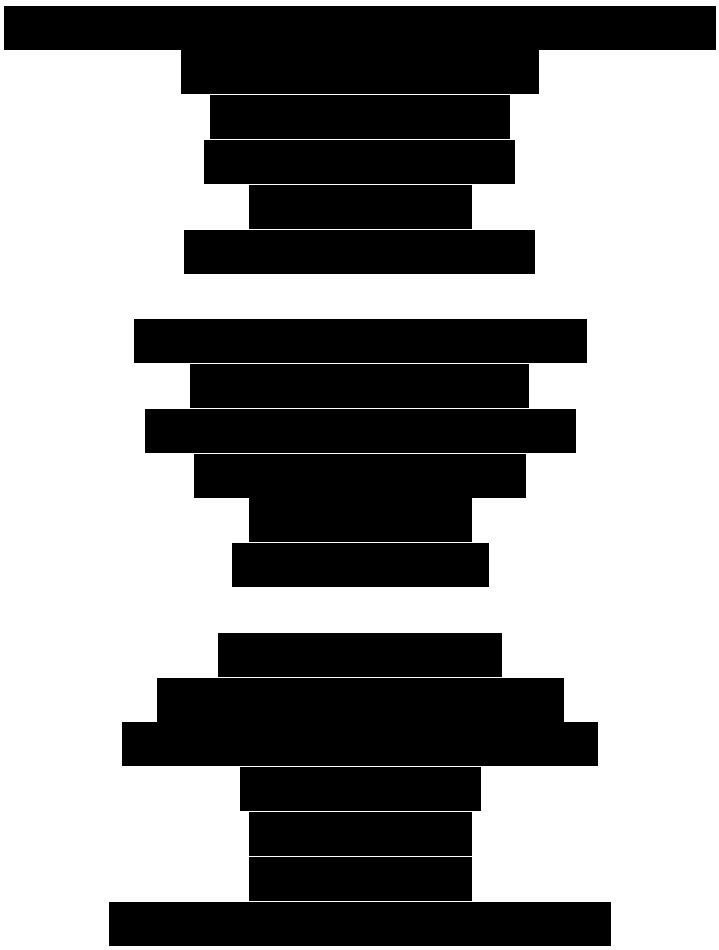
**Participating Centers**



Protocol #115523 (ARN-509-002) Study Drug: ARN-509

Sponsor Approval

Protocol ARN-509-002, Version 15.0, Amendment 9, 01 February 2019

Protocol Title: The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed Hormone Sensitive Prostate Cancer

Electronic signature appended at the end of the protocol

[redacted]

06 Feb 2019

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Date



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**Protocol Agreement**

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practice (GCP), as described in the United States Code of Federal Regulation (CFR) 21 Parts 11, 50, 54, 56, and 312 and the appropriate International Conference on Harmonisation guidance documents.

**Protocol:** ARN-509-002, Version 15.0, Amendment 9, 01 February 2019

**Protocol Title:** The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed Hormone Sensitive Prostate Cancer

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*Investigator Signature* *Date*

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*Print Name and Title*

*Site #* _____

*Site Name* _____

# ABSTRACT

| Title | **The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed Hormone Sensitive Prostate Cancer** |
|---|---|
| Study population | Key Eligibility Criteria:<br>• Histologically proven adenocarcinoma of the prostate<br>• Rising PSA after prior definitive local therapy (radical prostatectomy, external beam radiation, or brachytherapy) or combination of radical prostatectomy and radiotherapy<br>• Prior primary or salvage radiation or not a candidate for localized salvage radiation due to subject preference or clinical assessment based upon disease characteristics and/or subject co-morbidities.<br>• PSA doubling time ≤12 months<br>• No evidence of metastatic disease by computed tomography (CT)/magnetic resonance imaging (MRI) abdomen/pelvis and whole body bone scan. Abdominal/pelvic lymph nodes measuring less than or equal to 2 cm in short axis are allowed.<br>• Minimum PSA 1.0 ng/mL if prior radical prostatectomy +/- adjuvant or salvage radiation; nadir + 2.0 ng/mL if prior RT without prior radical prostatectomy<br>• No androgen deprivation therapy (ADT) within 6 months prior to randomization<br>• No prior ADT for biochemical relapse<br>• No 5-alpha reductase inhibitor or anti-androgen within 6 weeks prior to randomization<br>• Prior chemotherapy is allowed only in the (neo) adjuvant setting, and if last dose was >6 months prior to randomization<br>• Serum testosterone ≥ 150 ng/dL<br>• No prior use of bone-modifying agent within 3 months prior to randomization<br>• QTc interval ≤ 480 msec<br>• No history of seizures or medical conditions, which may lower seizure threshold |
| Rationale for Study | Prostate cancer patients with biochemical relapse (BCR), and a PSA doubling time (PSADT) of 12 months or lower represent a subset of patients at significant risk for the development of metastases and prostate cancer-specific mortality. In general, ADT is an appropriate approach for these patients, but carries risks of its own, including a potential impact on quality of life (QOL), and the potential for clinically significant metabolic derangements. Consequently, new strategies that can mitigate these adverse effects represent an important unmet need. Two potential strategies in this group of patients are a) to utilize a highly active second generation androgen receptor (AR) inhibitor as monotherapy and b) to add a highly active second generation AR inhibitor to conventional luteinizing hormone releasing hormone (LHRH) agonist (LHRHa) intermittent androgen deprivation (IADT). The first approach is predicated on the expectation that AR inhibitor monotherapy will have fewer adverse events, while the second approach is based on the expectation that more effective combination therapy will result in greater anti-cancer activity, and consequently, after a finite period of therapy, allow a longer period of time off ADT (and hence improved QOL) as part of an intermittent ADT approach.<br>The proposed clinical trial will study the effects of 12 months of therapy with ARN-509 (a highly potent second generation AR antagonist) alone, or in combination with an LHRHa, each compared with LHRHa alone, in men with a rapidly rising serum PSA after prior definitive local therapy for prostate cancer. Endpoints selected reflect measurable short-term effects of ADT, including QOL and several metabolic parameters. In addition, the relative effect of each treatment strategy on PSA suppression as well as testosterone recovery (and subsequent PSA progression) after 12 months of therapy will be evaluated. Favorable results suggesting an improvement in QOL for either strategy will provide justification for larger definitive trials of second generation AR inhibitors as a treatment alternative or addition to LHRHa therapy in the BCR disease population. |

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| Primary Objectives | • To compare the mean change from baseline in QOL as measured by total FACT-P score over a period of 12 months of therapy with ARN-509 monotherapy vs. LHRHa monotherapy in men with BCR to test for superiority with ARN-509 monotherapy<br>• To compare the mean change from baseline in QOL as measured by total FACT-P score over a period of 12 months of therapy of ARN-509 + LHRHa vs. LHRHa monotherapy in men with BCR to test for non-inferiority with ARN-509 + LHRHa |
| Secondary Objectives | • Other Quality of Life Instruments: To compare (a) ARN-509 monotherapy vs. LHRHa monotherapy and (b) ARN-509 + LHRHa vs. LHRHa monotherapy with regards to change over time in QOL<br>• To compare (a) ARN-509 monotherapy vs. LHRHa monotherapy and (b) ARN-509 + LHRHa vs. LHRHa monotherapy with regards to PSA modulation:<br>• To compare (a) ARN-509 monotherapy vs. LHRHa monotherapy and (b) ARN-509 + LHRHa vs. LHRHa monotherapy with regards to metabolic and hormonal effects:<br>• To characterize the safety profile of ARN-509 monotherapy and in combination with LHRHa.<br>• Biomarker analyses will be conducted on formalin-fixed paraffin-embedded (FFPE) blocks or slides, plasma, and whole blood samples collected from consented subjects to assess $AR^{F876L}$ mutation and other resistance markers from all 3 treatment groups. |

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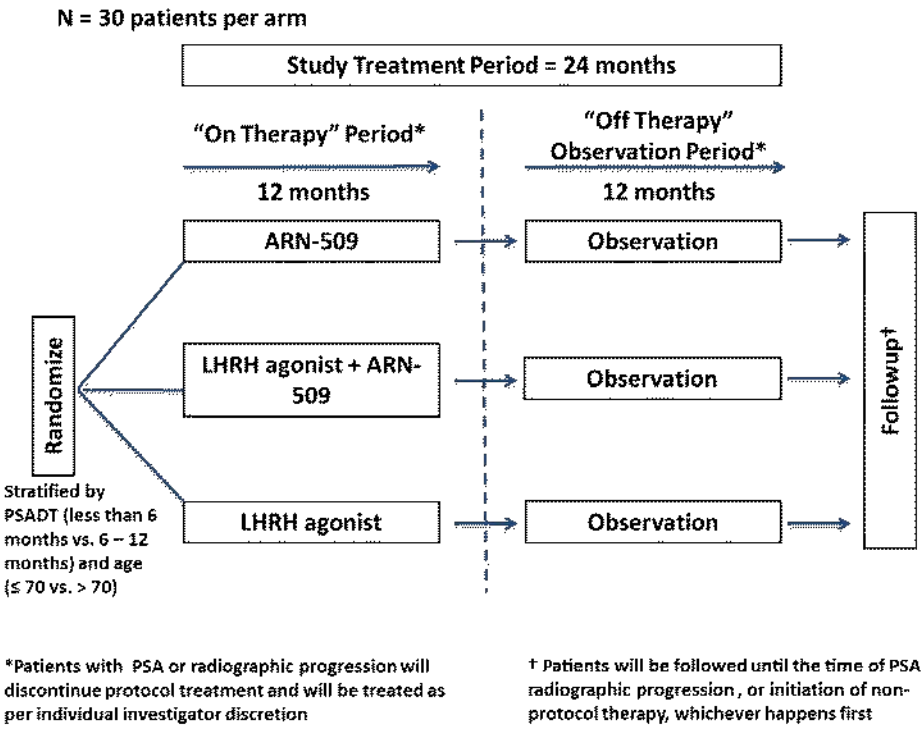
| Study Design | Phase 2, randomized, open-label 3-arm multicenter study evaluating 12 months of treatment with LHRHa monotherapy, ARN-509 monotherapy, or the combination in men with non-metastatic biochemically relapsed prostate cancer with rapidly rising PSA levels after prior definitive therapy for localized prostate cancer. Subjects will be stratified by PSADT (< 6 months vs. 6-12 months) and age (≤ 70 vs. > 70) and randomized with equal probability from within each of the 4 strata to 1 of the 3 study arms. There will be 2 periods of 12 months each in the 24 month-long treatment period: (1) an On-therapy Period lasting 12 months, during which time subjects receive randomly assigned protocol therapy, and (2) an Off-therapy Observation Period also lasting 12 months.<br><br>  |
| Number of subjects | Ninety men, with a rising serum PSA after prior definitive therapy including radical prostatectomy and/or radiation therapy, who have a PSADT of less than or equal to 12 months, will be enrolled. |
| Duration of Therapy | Subjects will receive protocol therapy for a maximum of 12 months, or shorter duration if evidence of PSA/radiographic progression or unacceptable toxicity during protocol therapy or subject/physician withdrawal from the study. If there is no evidence of disease progression after 12 months of protocol therapy, subjects will enter the therapy Off-therapy Observation period (Months 13-24). |
| Duration of Follow up | If there is no evidence of PSA or radiographic progression after 24 months from Day 1 of the On-Treatment Period, subjects will enter a Follow-up Period. Subjects will remain on study until the time of PSA or radiographic progression or initiation of non-protocol therapy or subject/physician withdrawal from the study, whichever occurs first. Subjects in the Follow-up Period will be discontinued at the time of the final clinical cutoff described in the following section. |
| Duration of study | With estimated accrual duration of 12 months, the data-cutoff for analysis of primary and secondary endpoints will be at 36 months from the time the study opens to accrual. The Sponsor will establish a final clinical cutoff date after all subjects have completed the Month 24 Visit. Data collection will cease at this time. The final clinical study report will be written based on these data. The total study duration is 6 years; the last patient was consented at 4 years and the final clinical cutoff is 2 years (24 months) after last patient was consented. |

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| Study Drugs | **1. ARN-509**<br>With Amendment 7 (Version 8.0), subjects receiving the softgel capsules will switch to tablets starting at the next cycle and all newly enrolled subjects will receive tablets.<br>Drug Substance: ARN-509 drug substance is an almost white to slightly brown powder.<br>Formulation: The ARN-509 tablet supplied for this study contains 60 mg of JNJ-56021927. It will be manufactured and provided under the responsibility of the Sponsor.<br>Dose and Route of Administration: ARN-509 will be administered orally on a continuous daily dosing regimen at a dose of 240 mg per day (4 x 60-mg tablets) with or without food.<br>**2. LHRH Agonist**<br>Choice of specific LHRHa to be used in this study will be per investigator discretion/site practice guidelines. Options include Eligard®, Lupron Depot®, Zoladex®, or Trelstar®. Dosing schedule will be per individual investigator discretion. The use of LHRH antagonists (e.g. degarelix) will not be permitted.<br>Route of Administration: The LHRHa injections will be delivered either subcutaneously (Eligard®, Zoladex®) or intramuscularly (Lupron Depot®, Trelstar®) by a trained health care provider while on protocol therapy. |
| Safety Assessments | Safety Assessments: During each monthly study visit during protocol therapy, the maximum grade observed for each toxicity will be tabulated, as graded by National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.<br>Interim Safety Review: Will be performed after 20 subjects have completed at least 1 month of therapy with either ARN-509 monotherapy or ARN-509 + LHRHa. If there are > 5 subjects with Grade 3 or higher toxicities not typically related to ADT, that the study investigator deems as possibly, probably, or definitely treatment-related, the study will be terminated. Study accrual will continue during the interim safety review. |
| Study Endpoints | Primary Endpoint: Mean change from baseline in total FACT-P score at 12 months<br>Secondary Endpoints:<br>*Additional Quality of Life Measures:*<br>• Mean change from baseline in total FACT-P, EORTC QLQ-C30/PR25, and SHIM scores over time<br>*PSA Modulation:*<br>• Time to PSA progression<br>• Proportion of subjects without PSA or radiographic progression and recovery of serum testosterone to > 150 ng/dL at 24 months.<br>• Proportion of subjects with a serum PSA < 0.2 ng/mL after 7 months of protocol therapy<br>*Metabolic and Hormonal:*<br>• Mean change from baseline in markers of insulin resistance (BMI, fasting glucose/insulin, hemoglobin A1C), fasting lipids, bone mineral density (as measured by DEXA at the femoral neck, and lumbar spine) over time<br>• Time to testosterone recovery to > 50 ng/dL and > 150 ng/dL during the Off-therapy Observation Period<br>• Mean change from baseline in serum DHT and estradiol levels over time<br>*Safety:*<br>• Incidence and severity of adverse events<br>• Abnormal findings in physical exams and laboratory tests<br>Correlative studies<br>• Frequency of subjects emerging with ARF876L mutation at the end of treatment and progression.<br>• Frequency of subjects expressing various RNA markers previously demonstrated to confer resistance ARN-509 at baseline, end of treatment, and progression |

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| Unique Aspects of the Study | This study represents the first clinical trial investigating the use of ARN-509, a potent, second generation AR antagonist in a hormone-sensitive prostate cancer disease population. Furthermore, the study endpoints, including QOL and changes in metabolic markers represent clinically relevant, measurable study endpoints, which can be utilized in initial Phase 2 randomized trials comparing novel treatment paradigms vs. standard ADT in biochemically relapsed disease as a means of justifying the further study of a novel agent in this disease setting. |

## List of Abbreviations

| | |
|---|---|
| ADT | androgen deprivation therapy |
| AlkP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AR | androgen receptor |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| ASTRO | American Society for Therapeutic Radiology and Oncology |
| BCR | biochemical relapse |
| BMD | bone mineral density |
| BMI | body mass index |
| CAB | combined androgen blockade |
| CBC | complete blood count |
| CI | confidence interval |
| eCRF | electronic case report form |
| CRPC | castrate-resistant prostate cancer |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DAO | data as observed |
| DEXA | dual energy x-ray absorptiometry |
| DHT | dihydrotestosterone |
| DLT | dose-limiting toxicity |
| ECOG | Eastern Cooperative Oncology Group |
| eDC | electronic data capture |
| EORTC | European Organization for Research and Treatment of Cancer |
| FACT-P | Functional Assessment of Cancer Therapy – Prostate |
| FDA | Food and Drug Administration |
| FFPE | formalin-fixed paraffin-embedded |
| HDL | high-density lipoprotein |
| HR | hazard ratio |
| IADT | intermittent androgen deprivation therapy |
| ITT | intent-to-treat |

| | |
|---|---|
| LDL | low-density lipoprotein |
| LHRH | luteinizing hormone-releasing hormone |
| LHRHa | LHRH agonist |
| MRI | magnetic resonance imaging |
| NCI | National Cancer Institute |
| NCIC | National Cancer Institute of Canada |
| OS | overall survival |
| PAB | peripheral androgen blockade |
| PBMC | peripheral blood mononuclear cells |
| PQC | product quality complaint |
| PSA | prostate-specific antigen |
| PSADT | PSA doubling time |
| QOL | quality of life |
| RT | radiation therapy |
| RTOG | Radiation Therapy Oncology Group |
| TSH | thyroid stimulating hormone |
| SHIM | Sexual Health Inventory for Men |

**Table of Contents**

## PROTOCOL AMENDMENTS

| Protocol Version | Issue Date |
|---|---|
| Original Protocol | 20 November 2011 |
| Amendment 1 | 11 January 2012 |
| Amendment 2 | 13 April 2012 |
| Amendment 3 | 7 June 2012 |
| Amendment 4 | 31 January 2013 |
| Amendment 5 | 3 June 2014 |
| Amendment 6 | 12 September 2014 |
| Amendment 7 | 30 September 2015 |
| Amendment 8 | 16 August 2016 |
| Amendment 9 | 01 February 2019 |

*All previous amendment changes are provided in separate summary documents (EDMS-ERI-83833142)

Amendments are listed beginning with the most recent amendment.

**Amendment 9 (01 February 2019)**

**The overall reasons for the amendment:** The protocol was amended to clarify the time of the final clinical cutoff and to refer to the central laboratories generically rather than specifically name these centers.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Clarified the time of the final clinical cutoff date and that subjects continuing in the Follow-up Period at this time will be discontinued. | |
| Abstract, Duration of Follow up;<br>Abstract, Duration of Study;<br>3.1 Overall Study Characteristics;<br>11.2 Interim Analysis | The Abstract (under Duration of Study), explains that the Sponsor will establish a final clinical cutoff date after all subjects have completed the Month 24 Visit. Data collection will cease at this time. The final clinical study report will be written based on these data. Clarified that the total study duration is 6 years, ie, the last patient was consented at 4 years and the final clinical cutoff is 2 years (24 months) after last patient was consented. The 6-year study duration (previously 5 years) was also mentioned in Section 3.1. In the body of the protocol, this information has been placed in new Section 11.2.2. The original information under Section 11.2 (titled Interim Analysis) was placed under new Section 11.2.1 and Subheader 11.2 was retitled Clinical Cutoffs. Also, the Abstract (under Duration of Follow Up) and Sections 3.1 and 11.2.2, note that subjects in the Follow-up Period will be discontinued at the time of the final clinical cutoff (and the appropriate section is referenced for additional information in the Abstract and in Section 3.1). |
| **Rationale:** Specific laboratory names and information related to a specific laboratory were removed, as the storage location for specimens has changed. | |
| Appendix 6 | Mentions of USCF and LabConnect were replaced with “a central laboratory” and the following sentences were removed from the fourth paragraph of this appendix: “Specimen and data registries will be kept by the UCSF-HDFCCC. This registry will have a coordinated database to protect subject confidentiality and safety.” |

**Amendment 8 (16 August 2016)**

**The overall reasons for the amendment:** The main reason for the amendment is to add collection of optional archival formalin-fixed (FFPE) blocks or slides in order to gain understanding of biology and identify markers associated with response or resistance to complete androgen annihilation (apalutamide+ luteinizing hormone releasing hormone agonist [LHRHa]) compared with apalutamide or LHRHa alone.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Optional archival FFPE blocks or slides were added as samples for biomarker research. | |
| Abstract Secondary Objectives; 2.3.2 Secondary Objectives; 6.4.2.4 Correlative Studies: Exploratory Biomarkers; 7.1 Study Schedule: On-therapy Period (Day 1-Month 12); 7.5.1 Day 1 of Study Treatment; 10.7 Optional Sample Collection for Banking, RNA, and Biomarker Analysis; 11.4.2 Analytic Plan for Secondary Endpoints; Appendix 6 (Sections V & VI) | Added language for inclusion of archival FFPE blocks or slides. |
| **Rationale:** The PSA modulation endpoint will not be analyzed using a Kaplan-Meier approach. | |
| 11.4.2.Analytic Plan for Secondary Endpoints | The following revision was made: The proportions by treatment will be ~~estimated using the Kaplan Meier approach to account for censoring and then be~~ compared using the chi square test or Fisher's exact test as appropriate. Results will be summarized at 24 months from Day 1 with 95% confidence intervals for each treatment arm. Subjects who withdraw from the study prior to 24 months after Day 1 will **not** be **included** ~~censored~~ in this analysis. ~~Different censoring rules may be applied as sensitivity analyses.~~ Details can be found in the statistical analysis plan (SAP). |
| **Rationale:** Minor revision to description of analysis of secondary endpoints. | |
| 11.4.2 Analytic Plan for Secondary Endpoints | Removed "product limit" method for description of Kaplan-Meier, the additional language is redundant terminology. |
| **Rationale:** Secondary objective for biomarkers in Section 2.3.2 did not match the abstract. | |
| 2.3.2 Secondary Objectives | Matched wording in Section 2.3.2 and abstract. |
| **Rationale:** Allow more time to obtain laboratory assessments before study visits. | |
| 7.1 Study Schedule: On-therapy Period (Day 1-Month 12) | Added the following to footnote 3: **Window for laboratory assessments before study visits is -7 days.** |

| Applicable Section(s) | Description of Change(s) |
|---|---|

**Amendment 7 (30 September 2015)**

**The overall reasons for the amendment:** The main reason for this amendment is to switch softgel capsules to tablets (commercial formulation) for subjects currently receiving the softgel capsules and to administer tablets to newly enrolled subjects. Updated drug-drug interaction language and other recent updates to standard wording in ARN-509 protocols were incorporated, where relevant. Editorial changes made throughout to remove redundancy and improve clarity.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Switch of softgel capsules to tablets is incorporated. Vitamin E is not included in the tablet formulation. Twice daily dosing is no longer needed with the tablet formulation because of the reduced pill burden and change in excipients. | |
| Throughout | Changed "softgel capsules" or "capsules" to "tablets." |
| Abstract Study Drugs 1. ARN-509; Section 7.5.3 ARN-509; Section 8.1 ARN-509 | Replaced all information on the capsules with information on the tablets. Added instructions for the switch from softgel capsules to tablets for subjects receiving softgel capsules and for subjects who enroll on or after implementation of this amendment. A table was included in Section 8.1 showing the conversion from capsule to tablet and clarifying that the conversion is 2:1. |
| Section 7.5.4.3 Restricted Medications; Section 8.1 ARN-509: Section 9.2 Dose Modifications for ARN-509; Appendix 5 | Removed vitamin E restrictions, no longer applicable with the tablet formulation. |
| Section 9.2 Dose Modifications for ARN-509 | Revised the dose modification section for alignment with other ARN-509 protocols and to incorporate changes for the switch from softgel capsules to tablets. |
| **Rationale:** For all eligibility criteria with a timing interval , the interval was revised to be relative to randomization rather than study entry, which is consistent with other ARN-509 protocols. | |
| Abstract Study Population; Section 4.2 Inclusion Criteria; Section 4.3 Exclusion Criteria; Section 6.1 Rationale for the Study Population | Revised Inclusion Criteria # 6, 8, and 16 and Exclusion Criteria 1, 2, 4, 5, 6, 7, and 8. Made corresponding revisions in the abstract. |
| **Rationale:** Revised objectives and endpoints for better clarity, consistency, and to allow more flexibility regarding evaluating changes over time. | |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Abstract Primary Objectives, Secondary Objectives, Study Endpoints; Section 2.3.1 Primary Objectives; Section 2.3.2 Secondary Objectives; Section 6.4.1 Primary Endpoint; Section 6.4.2 Secondary Endpoints | Modified to include "changes from baseline" and over a period of time rather than specific timelines. Simplified the objectives and removed "endpoint" information. |
| **Rationale:** Revised the hypotheses for consistency with the revisions to the objectives and endpoints | |
| Section 2.1 Hypothesis #1; Section 2.2 Hypothesis #2 | Minor editorial revisions were made for consistency with objectives and endpoints and consistency between the 2 hypotheses. |
| **Rationale:** Updated information on drug-drug interactions based on new information. | |
| Section 7.5.4.3 ARN-509: Restricted Medications, Appendix 5 | Deleted current wording on CYP3A4 and CYP2C8 drug-drug interactions, refer to Appendix 5. Updated Appendix 5 with new information. |
| **Rationale:** Revisions to the study schedules were incorporated for improved clarity and for consistency with other sections of the protocol. Additional changes were also incorporated into the Study Schedules as outlined. | |
| Section 7.1, Study Schedule On-therapy Period (Day 1-Month 12); Section 7.2, Study Schedule Off-therapy Therapy Observation Period (Months 13-24) and Follow-up Period (Month 25+) | Revised footnotes, as needed for consistency with other sections of the protocol or because of changes in other sections. For both study schedules clarified that the Progression Visits take place at the time of progression if progression occurs before the end of the period.<br>Additional "optional" when referring to the samples collected for banking, RNA, and biomarker research.<br>Checked for consistency across the 2 schedules. In some cases, an "X" was placed in a manner that was inconsistent. For example, if an assessment was to occur at each monthly visit (On-therapy Period) or every 2 months (Off-therapy Period), it would also cover the other monthly visits, therefore an additional "X" was not needed. |
| Section 7.1, Study Schedule On-therapy Period (Day 1-Month 12) | Added a row for the collection of concomitant medications.<br>In order to have sufficient study drug supply for each "monthly" visit (28-day, 28-day, 35-day sequence) of therapy, the visit window was reduced from ±7 days to ±2 days.<br>Revised the timing for collection of optional samples to Day 1 rather than screening. Clarified that these samples and serum PSA sample should be taken predose.<br>Revised footnote "5" for timing of visits. All subjects should be following a 28-day, 28-day, 35-day schedule (±2 days).<br>For subjects who discontinue therapy without proceeding to the Off-therapy Period, AE reporting should continue until 30 days after the last dose of protocol therapy. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Section 7.2, Study Schedule Off-therapy Therapy Observation Period (Months 13-24) and Follow-up Period (Month 25+); | Revised heading for the Follow-up Period from Month 24+ to Month 25+. |
| **Rationale:** Several sections contained redundant information. For improved clarity and to avoid the need to make changes in several sections of the protocols with amendments, these sections were edited. The studies activities sections were condensed and made consistent with the Study Schedules. | |
| Section 7.3 Screening Period/Pre-study Evaluation; Section 7.5 Study Period 1: On-therapy Period (Month 1 to 12); Section 7.6 Study Period II: Off-therapy Period (Months 13 to 24); Section 7.7 Follow-up Period (Month 25+); previous Section 12.2 Accrual | Revisions were made in each of these sections to ensure to consistency with the Study Schedules and to remove redundancy. Section 12.2 Accrual was removed because the information was redundant . |
| **Rationale:** The statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used in analyzing the data is outlined in the protocol. Details will be provided in the Statistical Analysis Plan (SAP). Approaches for analysis of repeated measures will be used to account for multiple data points from the same subjects and potential missing records. | |
| Section 11 Planned Statistical Methods; Section 11.4.1 Analytic Plan for the Primary Endpoint; Section 11.4.2 Analytic Plan for the Secondary Endpoints; removed Section 10.6 Demographics and Baseline Characteristics | Added sentence to Section 11 stating that the sponsor will be performing the statistical analysis and that details will be provided in the SAP.<br>Primary and secondary endpoints (QOL, metabolic and hormonal parameters) will be analyzed using a mixed model for repeated measures (MMRM).<br>Abnormal findings in physical exams and laboratory tests will be summarized.<br>Removed Section 10.6, details will be provided in the SAP. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** It is preferable, but not required to have the PSA evaluations obtained from the same laboratory. | |
| Section 4.2 Inclusion Criteria, Criterion #5; Section 7.1 Study Schedule On-Therapy Period (Day 1-Month 12); Section 7.2 Study Schedule Off-therapy Observation Period (Month 13-24) and Follow-up Period (Month 25+); Section 7.3.2 Laboratory; Section 10.6 PSA Measurements | Added wording that it be preferable to have the PSA evaluations obtained from the same laboratory. |
| **Rationale:** The Investigator's Brochure should be the source for the most up to date Reference Safety Information for ARN-509. The applicable product insert or summary of product characteristics should be source for safety information on LHRH agonists | |
| Section 1.4 Second Generation AR Antagonists in BCR Hormone Sensitive Prostate Cancer; Section 8.1 ARN-509 Section 8.2 LHRH Agonist | Removed safety information and add reference to the Investigator's Brochure. Added source information for the safety information on LHRH agonists. |
| Section 12.1.3 Expectedness | Removed wording that was not consistent with other ARN-509 protocols. Added the following for LHRH agonist therapy: For LHRHa with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the applicable package insert or summary of product characteristics. |
| **Rationale:** Subject initials should not be used for identification purposes | |
| Section 14.1 Data Collection Instruments; Section 14.6 Subject Confidentiality; Section 15 Administrative, Ethical, Regulatory Considerations | Reference to subject initials was removed. |
| **Rationale:** Refer to Appendix 6 for details on collection, processing, and shipping of peripheral blood and urine samples to avoid repetition and need for updating in several sections of the protocol if changes occur. | |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Section 7.1, Study Schedule On-therapy Period (Day 1-Month 12); Section 7.2, Study Schedule Off-therapy Observation Period (Months 13-24) and Follow-up Period (+25 Months); Section 7.3.2 Laboratory Assessments; Section 7.5.7 Laboratory Assessments; Section 7.6.3 Laboratory Assessments; Section 7.7 Follow up Period (±25 months) | Removed details and refer to Appendix 6. |
| **Rationale:** Updated eligibility criteria and added a prohibitions and restrictions section regarding sexual activity for consistency with other protocols. | |
| Section 4.2 Inclusion Criteria; Section 4.3 Exclusion Criteria | Updated Inclusion Criterion #17, removed Exclusion Criterion #11. Added Section 5 Prohibitions and Restrictions and updated numbering for the subsequent sections. |
| **Rationale:** Limited discussion of nonclinical and clinical data to ARN-509 as this study is providing no comparison with enzalutamide. | |
| Section 1.4 Second Generation AR Antagonists in BCR Hormone Sensitive Prostate Cancer | Removed enzalutamide data from this section and removed references from the reference list. |
| **Rationale:** Updated references | |
| References | Updated Rathkopf abstract with publication (Ref#32), removed outdated Investigator's Brochure reference, and removed enzalutamide references. |
| **Rationale:** Minor edits were made for improved clarity or to correct a formatting or typographical error. | |
| Throughout | Minor edits, formatting or corrections. |

**Amendment 6 (12 September 2014)**

**The overall reasons for the amendment:** Incorporate investigator feedback to improve the quality and clarity of the protocol. Revisions to several eligibility criteria were made to improve clarity, to increase enrollment or for consistency with the informed consent form. Additional revisions were made to the safety section for consistency with the Spongsor's standard protocol template language. Changes in data management were also incorporated.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Eligibility criteria were numbered to align with the electronic case report form (eCRF) and several criteria were modified to improve clarity and to help increase enrollment. Added eligibility criteria for required contraception and timing before donation of sperm or fathering children for consistency with the informed consent form. Changes also affected other sections of the protocol. | |
| Abstract; Section 4.2, Inclusion Criteria | Criterion # 5: Revised to include all recorded PSA values obtained over the past 6 months instead of 12 months.<br>Criterion #6: Clarified the description of lymph node size.<br>Criterion # 8 Changed from 12 months to 6 months<br>Added Criterion #16 |
| Abstract; Section 4.3, Exclusion Criteria; Section 6.3.2, Laboratory (within 14 days prior to treatment initiation)<br>Section 6.3.4, Radiographic Studies (within 12 weeks prior to treatment initiation);<br>Section 6.5.4, Concomitant Medications | Criterion #1: Changed from 3 months to 6 weeks.<br>Criterion #2: Changed from 12 months to 6 weeks.<br>Criterion #4 Changed from 12 months to 6 months and removed redundant wording<br>Criterion #8: Clarified exclusion for use of bone-modifying agents and timing, and removed the requirement for osteoporosis assessement |
| Section 4.2, Inclusion Criteria; Section 4.3, Exclusion Criteria | Added Inclusion Criterion #17: Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.<br><br>Added Exclusion Criterion #11: Subject plans to father a child while enrolled in this study or within 3 months after the last dose of study drug |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Per investigator feedback, the Study Schedules were modified for greater clarity. Revisions were also made as needed in other sections of the protocol. | |
| Section 3.1, Overall Study Characteristics; Section 6.1, Study Schedule "On Therapy" Period (Day 1-Month 12); Section 6.2, Study Schedule "Off Therapy" Observation Period (Months 13-24) and Follow-up Period (+24 Months); Section 6.5.8, Duration of Therapy "On Therapy" Period; Section 6.6.4, Duration of "Off Therapy" Observation Period | In addition to minor edits, footnotes to the Study Schedules were revised and reworded for greater clarity.<br>Additional instructions for follow-up period (24+ months) were included for subjects who discontinue in the absence of progressive disease. |
| **Rationale**: Consistency between Study Schedule and subsections in Section 6 were not consistent | |
| All subsections of Section 6, Study Activities | All subsections were checked against the Study Schedules to ensure consistency. |
| **Rationale:** Description of study periods and timing of assessments were inconsistent. | |
| Throughout the protocol | Revised for consistency in the description of the study periods (ie "on therapy" period and "off therapy" observation period). Revised description of the timing of assessments for greater clarity and consistency. |
| **Rationale:** Clarified that the 3 month schedule be such that treatment period completes at exactly 12 months | |
| Section 6.1, Study Schedule "On Therapy" Period (Day 1-Month 12); Section 6.5.3, ARN-509; Section 6.5.8, Duration of Therapy "On Therapy" Period | Added text:<br>To align ARN-509 monthly dosing with LHRHa treatment on a 3-month schedule, the visits should be divided into 28-days, 28-days, and 35-days. This ensures an exact 12 month treatment period. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** More information provided for the radiographic progression-free survival endpoint. Only Investigator review will be used to assess radiographic progression-free survival. | |
| Section 6.3.3 Radiographic Studies (within 6 weeks prior to treatment initiation); Section 6.5.7 Radiographic Assessment; Section 6.6.3, Radiographic Assessment | Added text:<br>Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast or without, as long as method is identical each time new scans are done.<br>There will be no central reading of the scans and radiographic progression will be based upon investigator assessment |
| **Rationale:** Added thyroid stimulating hormone (TSH) to laboratory evaluations during treatment per request of the Investigational Review Board (IRB) | |
| Section 6.1, Study Schedule "On Therapy" Period (Day 1-Month 12); add other sections; Section 6.3.2, Laboratory (within 14 days prior to treatment initiation) Section 6.5.6, Laboratory Assessments (±7 days) | Added separate column for timing of TSH laboratory evaluation to the study schedule and separate bullets in the other sections. |
| Rationale: The window for the scheduled luteinizing hormone releasing hormone agonist (LHRHa) injection was changed from ±14 days to ±7 days. | |
| Section 6.1, Study Schedule "On Therapy" Period (Day 1-Month 12); Section 6.5.2, LHRH Agonist | If a subject does not receive a scheduled LHRHa injection within ±7 days of the scheduled due date for injection, he will be removed from study. |
| **Rationale:** Height is measured only at the screening visit. | |
| Section 6.5.1, Day 1 of Study Treatment | Height was removed. |
| **Rationale:** Added language to ensure that collection of QOL information is completed during for subjects who discontinue therapy prior to Month 12. | |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Section 6.5.8, Duration of "On Therapy" Period | Added text: Efforts will be made to ensure that subjects who develop progressive disease or unacceptable toxicity prior to Month 12 still complete QOL scales at 3 and 12 months. |
| **Rationale:** Clarification of sample collection during the follow-up period. | |
| Section 6.7, Follow-up Period (24+ Months) | Added text: If no progressive disease occurred during Months 1 to 24 and it occurred during the follow-up period, whole blood RNA and Plasma for banking samples need to be collected during the follow-up period. These samples will be shipped to UCSF, banked, and subsequently analyzed (see Appendix 6 for collection/shipping instructions). Data entry needs to occur on the follow-up visit in which the progressive disease was observed. |
| **Rationale:** Dose medication for toxicity related to ARN-509 was clarified. | |
| Section 8.2, Dose Modification for ARN-509. | Revised previous text to read:<br>For subjects receiving ARN-509 (with or without LHRHa) and who experience Grade 1 or 2 adverse events related to study therapy, the decision to change ARN-509 dosing from QD to BID dosing, to delay treatment ("treatment break" of maximum 28 days), dose reduce (to 180 mg QD, no lower dose allowed) or to discontinue treatment in such a situation will be per individual investigator discretion. |
| **Rationale:** Revisions to data collection plans and addition of procedures for corrections to the electronic case report form (eCRF). | |
| Section 13.1, Data Collection Instruments; 13.2, Data Quality Control and Reporting | Electronic data capture and other procedures for data collection have been updated.<br>Deleted the previous Section 13.2 Data Management Procedures. |
| **Rationale:** Correction made, DLTs are not being collected in this study, this is a Phase 2 study not Phase 1. | |
| Section 10.7.2, Secondary Endpoints | Removed the bullet: Incidence of DLT (Phase 1). |
| **Rationale:** In statistical method section, removed redundant text, revised analysis descriptions. | |
| Section 10.8, Methods for Analysis; Section 10.8.2, Analytic Plan for the Secondary Objectives | Revised the definition of the safety analysis population.<br>Revised the analysis description for the secondary objective (PSA Modulation).<br>Deleted redundant text. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Updated with new references | |
| Section 1.4, Second Generation AR Antagonist in BCR Hormone Sensitive Prostate cancer | Added reference #35. |
| Section 6.5.8, Duration of Therapy "On Therapy" Period | Added reference #64. |
| Throughout the protocol | Renumbered references, as relevant |
| Section 15, References | Added new references and renumbered, as relevant. |
| **Rationale:** Safety section updated for consistency with other Janssen protocols and the informed consent form. | |
| Section 11 | Updated this Section with standard Janssen template wording. |

**Amendment 5 (3 June 2014)**

**The overall reasons for the amendment:** The overall reasons for the amendment are to incorporate biomarker research, update sections for consistency with other protocols, update safety and publication section for alignment with the Janssen template and procedure, add reference and requirements for the DEXA scan, incorporate changes to Exclusion Criteria that were previously included in an addendum to the protocol. Other changes were also included for clarity or consistency.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** A biomarker research plan was incorporated. | |
| Abstract<br>2.3.2 Secondary Objectives | Biomarker analyses will be conducted on plasma and whole blood samples from all consented subjects to assess $AR^{F876L}$ mutations and other resistance markers from the 3 treatment groups |
| 5.4.2.4 Correlative Studies: Exploratory Biomarkers | Added Section 5.4.2.4 to the protocol |
| 6.1 Study Schedule<br>6.2 Study Schedule | Added columns for whole blood and plasma for biomarker testing. Added footnotes 7 and 10. |
| 6.3.2 Laboratory Assessments (within 14 days prior to treatment initiation);<br>6.5.6 Laboratory Assessments (±7 days); | Added information on sample collection. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 9.7 Optional Whole Blood and Plasma Collection for Biomarker Analysis | Added this new section. |
| 10.7.2 Secondary Endpoints;<br>10.8.2 Analytic Plan for the Secondary Objectives | Added biomarker analysis plan |
| 15. References | Added reference 62 |
| Appendix 6 | Added information on processing of samples. |
| **Rationale:** Exclusion criteria had previously been modified in an addendum, now incorporated into the protocol | |
| 4.3 Exclusion Criteria | Added clarification for bullet 4 regarding prior hormonal treatment with ADT<br>Added requirement for DEXA scan to bullet 8 |
| **Rationale:** Clarification of DEXA scan requirements and reference added | |
| Abstract, Study Endpoints<br>3.2.2 Secondary Endpoints<br>6 Study Activities<br>6.5.7 Radiographic Assessments<br>9.5.3 Bone Mineral Density<br>10.7.2 Secondary Endpoints<br>10.8.2 Analytic Plan for the Secondary Objectives | Removed total hip from DEXA scans |
| 6.1 Study Schedule | Added footnote 6 for timing of the baseline assessment<br>Added footnote 9 for reference |
| 6.3.4 Radiographic Studies | New section added with DEXA reference information |
| **Rationale:** Alignment of safety reporting and safety wording with Janssen protocol template and process. | |
| Throughout | Changed “toxicity” to safety when describing safety assessments or analyses. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) was mentioned frequently in the protocol and was updated to Version 4.03. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 6.1 Study Schedule; 6.5.5 Safety Assessment; 6.6.1 Safety Assessment | Clarified that reporting of adverse events starts with the signing of the informed consent form and that adverse events will be collected up to 30 days after the last dose of study medication.<br><br>Added footnote 8 to the Study Schedule |
| 6.5.5 Safety Assessment; 6.6.1 Safety Assessment 11.1.1 Adverse Events; 11.1.2 Serious Adverse Events; 11.1.4 Attribution; 11.1.6 Pregnancy; 11.5 Expedited Reporting | Incorporated Janssen protocol template wording. For Sections 6.5.5 and 6.6.1 the attribution wording was removed and a link to Section 11.1.4 was added. |
| **Rationale:** The safety analysis information included in the protocol was not sufficient. | |
| Abstract, Secondary Endpoints; 3.2.2 Secondary Endpoints; 10.7.2 Secondary Endpoints | Added more detail on the planned safety analysis |
| Rationale: Incorporation of product quality complaint handling | |
| 12. Product Quality Complaint Handling | Added a new section incorporating Janssen template wording and renumbered the subsequent sections of the protocol. |
| **Rationale:** Incorporation of Janssen use of information and publication policy | |
| 14.6 Use of Information and Publication | Revised this section to incorporate Janssen protocol template wording. |
| **Rationale:** For consistency across protocols, prohibited and restricted medication information while on ARN-509 treatment were incorporated into the protocol. | |
| 6.5.4.1 ARN-509: Prohibited Medications; 6.5.4.2 ARN-509: Restricted Medications | Added these sections to the protocol |
| **Rationale:** Updated study drug information and handling section. | |
| 7.1 ARN-509 | Added that clinical formulation-specific and batch-specific storage instructions can be found in the packaging label.<br>Under Drug Supply: added that ARN-509 is to be ordered directly from a designee indicated by the Sponsor.<br>Clarification of procedure for the return of clinical supplies. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Clarified timing for the completion of eCRFs following a visit or to address a query. | |
| 13.1 Data Collection Instruments | Previous wording "as soon as possible" was revised to 5 days |
| **Rationale:** This is the first protocol amendment since Aragon Pharmaceuticals, Inc became a wholly-owned subsidiary of Johnson & Johnson. The study chair has changed. | |
| Cover page | Updated the cover page to reflect the change for Aragon. Investigator list was updated. Added document repository number (page 2). |
| **Rationale:** Minor clarifications were made, as appropriate, based on feedback from investigators. | |
| Throughout | Revised wording as needed for greater clarity |

# 1 BACKGROUND

## 1.1 BIOCHEMICALLY RELAPSED PROSTATE CANCER

Prostate cancer is the second most common cancer in men worldwide, with an estimated incidence of 900,000 cases and 258,000 deaths in 2008 [1]. In the United States, approximately 222,000 cases were diagnosed in 2010 [2], of which an estimated two-thirds undergo radical prostatectomy or definitive radiation therapy (RT). Approximately 25%-35% of patients treated with definitive surgical or radiation therapy for localized adenocarcinoma of the prostate will recur in the form of rising serum PSA without overt metastatic disease, termed biochemical relapse (BCR) [3,4]. An estimated 40,000 - 50,000 men in the U.S develop biochemically relapsed prostate cancer each year, yet treatment of men in this disease state is far from standardized. The optimal time to initiate treatment and the choice of specific therapy for such patients remains controversial and highly variable in clinical practice. This may be due to several potential reasons, including (1) a dearth of prospective randomized trial data demonstrating an overall survival advantage for one particular therapeutic approach and (2) a biologically heterogeneous population with a variable natural disease course.

The kinetics of PSA change over time has emerged as an important independent prognostic factor for patients with BCR, both with respect to time to development of metastases as well as the risk of prostate cancer-specific mortality. In a cohort study of 8,669 men treated with localized therapy, of the 1,451 men with PSA recurrence, a PSA doubling time (PSADT) less than 3 months was associated with an approximately 50% chance of prostate-cancer specific mortality at 5 years; in contrast, those with a PSADT greater than 12 months had less than 10% prostate cancer-specific mortality during the same time interval [5]. In another study of 1,650 patients previously treated with external beam radiotherapy, at the time of PSA recurrence, the 3 year risk of distant metastases for a PSADT of 0-3 months, 3-6 months, 6-12 months, and > 12 months was 49%, 41%, 20%, and 7%, respectively (P <0 .001) [6].

## 1.2 RISK ADAPTED THERAPY FOR BCR PROSTATE CANCER PATIENTS

Risk stratifying patients with biochemical recurrence may allow for more optimal and individualized selection of treatment [7]. A prolonged PSADT, as well as other factors such as low Gleason grade, positive surgical margins, and pre-treatment PSA level < 2.0 ng/mL, may help to predict which patients may benefit from localized salvage therapy such as radiotherapy after prior prostatectomy [8]. For those patients with a PSADT greater than 12 months, active surveillance may be the optimal treatment approach, especially in elderly patients with other potentially life-limiting co-morbidities who are not candidates for locally directed salvage therapy. For patients with a very short PSADT, who are at significant risk of prostate-cancer specific mortality over the next 5-10 years, early treatment with continuous androgen deprivation therapy (ADT), in the form of luteinizing hormone releasing hormone (LHRH) agonists (eg, goserelin, leuprolide acetate) with or without an androgen receptor (AR) antagonist (eg, flutamide, bicalutamide), has been one standard approach.

There are no randomized data in this higher risk population demonstrating an overall survival advantage for early continuous ADT versus deferred therapy until the time of progression to metastatic disease. Nevertheless, retrospective data and extrapolation from randomized clinical trials of patients with high-risk localized disease (eg, node positive post-radical prostatectomy or

high risk radiation therapy patients) favor earlier treatment with ADT [9-11]. For example, in a prior clinical trial of 98 men with node-positive prostate cancer who have undergone prior radical prostatectomy and lymph node dissection, randomized to receive either immediate ADT or deferred until detection of distant metastases or symptomatic recurrences (ie, not started at the time of rising PSA only), men randomized to the immediate ADT arm showed a significant improvement in overall survival after a median follow up of 11.9 years (hazard ratio [HR] 1.84; 95% confidence interval [CI] 1.01-3.35, p = 0.04; median overall survival [OS] 13.9 vs. 11.3 years) [10]. In clinical trial RTOG 85-31, 173 prostate cancer patients with either clinical stage T3 or positive regional lymph nodes (radiographically or histologically) were randomized to receive either radiation therapy + immediate long term continuous ADT vs. RT + deferred ADT initiated at the time of disease relapse [9]. On multivariate analysis, RT + immediate ADT had a significant impact on absolute survival (p = 0.030), disease-specific failure (p = 0.014), metastatic failure (p = 0.005). While these studies are generally underpowered, and don't directly test the hypothesis of early vs. deferred ADT in the BCR patient population, they do raise a provocative question as to whether early ADT provides a clinical benefit in these patients.

## 1.3 THERAPEUTIC OPTIONS IN BCR PROSTATE CANCER PATIENTS

### 1.3.1 Combined Androgen Blockade (CAB)

Combined androgen blockade (CAB) refers to the combination of medical castration with an LHRH agonist (LHRHa) and a (first generation) antiandrogen such as flutamide or bicalutamide. There are currently no completed randomized clinical trials comparing CAB with LHRHa monotherapy in men with biochemically relapsed prostate cancer. In the metastatic hormone-sensitive disease population, several meta-analyses demonstrate a small 5 year overall survival benefit with the addition of a first generation antiandrogen to LHRHa therapy, with a slim absolute 5-year survival benefit of 2-3% [12, 13]. The American Society of Clinical Oncology (ASCO) guidelines state CAB can be considered as an option for the metastatic hormone-sensitive disease population [14]. In the non-metastatic BCR disease setting, the use of CAB is quite variable across clinical practices, ranging from no use to temporary use of antiandrogen at the time of initiation of ADT to continuous CAB.

While continuous, long term treatment with ADT is effective in terms of decreasing PSA levels, disease progression in the setting of castrate levels of testosterone is a near universal event. Furthermore, over the past decade, there has been a growing appreciation for the significant short-term and longer-term toxicities of continuous ADT, in which serum testosterone is maintained at a castrate level. Side effects developing shortly after the initiation of ADT include fatigue, gynecomastia, decreased libido, impotence, decreased physical capacity, mood changes, and hot flashes. Over the long term, serious metabolic side effects can often emerge, including decreased bone mineral density and risk for osteoporotic fractures, anemia, increased risk of insulin resistance and overt diabetes mellitus, dyslipidemia, and potentially, an increased risk of cardiovascular mortality [15-21].

### 1.3.2 Intermittent ADT (IADT)

Given the toxicities of long term, continuous ADT, more contemporary treatment strategies involving intermittent ADT (IADT) have emerged for men with BCR. The threshold at which to stop and start ADT during the course of IADT is variable in prior clinical trials and clinical

practice [22-25]. Nevertheless, numerous Phase 2 and 3 trials comparing IADT to continuous ADT, though not adequately powered for non-inferiority, have shown comparable overall and prostate-cancer specific survival and improved quality of life (QOL) [22-25]. More recently, a randomized Phase 3, non-inferiority trial of continuous vs. IADT in 1,386 patients with BCR after prior definitive radiation treatment was conducted by the NCIC. There was no difference in overall survival after a median follow up of 6.9 years (HR = 1.02, 95% CI 0.86 – 1.21) and significantly better QOL with IADT [26]. The results of this trial provide further justification to consider treatment alternatives to continuous ADT in the BCR disease setting.

### 1.3.3 Peripheral Androgen Blockade (PAB)

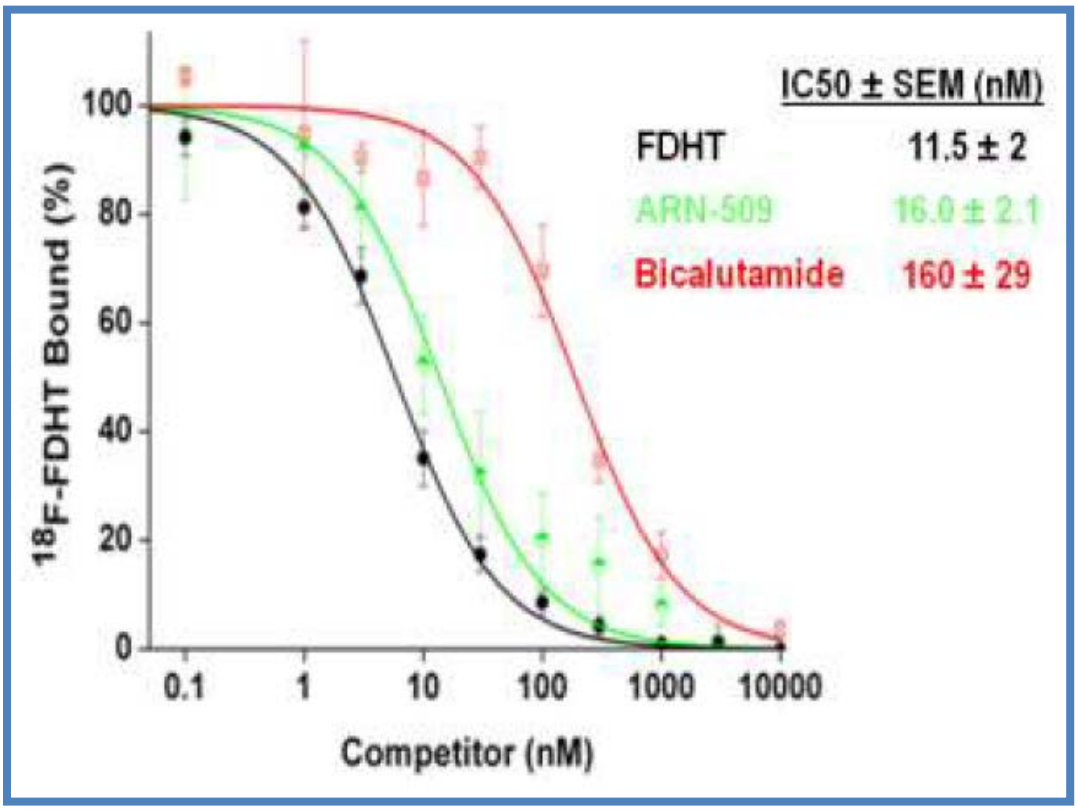
Peripheral androgen blockade, utilizing an androgen receptor antagonist (e.g. flutamide or bicalutamide), with or without a 5-alpha reductase inhibitor, inhibits intra-tumoral activation of the AR, thereby potentially slowing disease progression. Yet in contrast to ADT, PAB does not decrease serum testosterone levels to a castrate state. In theory, this may lead to an improvement in quality of life and the metabolic profile of patients treated with PAB versus traditional ADT, while hopefully preserving response to treatment. Preliminary data provide some support for this hypothesis. In a pooled analysis of 480 men with locally advanced (T3/T4 with serologic progression) non-metastatic prostate cancer and 805 men with metastatic prostate cancer randomized to high-dose bicalutamide versus medical or surgical castration, there was no statistical difference in overall survival between the two treatment groups (HR 1.05, p = 0.70). Those patients randomized to the bicalutamide therapy had improved quality of life with regards to sexual interest (p =0.029) and physical capacity (p = 0.046) compared with surgical castration [27]. Similarly in a separate (underpowered) study of 220 men with non-metastatic (n = 92) and metastatic (n = 128) prostate cancer randomized to receive either high-dose bicalutamide or ADT with flutamide plus goserelin, there was no detriment in overall survival and improved quality of life in the bicalutamide treatment arm [28]. In a more contemporary study, monotherapy with bicalutamide was compared to LHRHa therapy in patients with prostate cancer with no bone metastases. After 1 year of therapy, bicalutamide was shown to improve bone density (increase of 2.5% vs. decrease of 2.5% of bone density in the posterior-anterior lumbar spine), lessen increase in fat mass (6.4% vs. 11.1% increase), and diminish fatigue, loss of sexual interest and vasomotor flushing [29]. Although the earlier studies were underpowered, and additional metabolic profiling was not undertaken in this more recent study, in aggregate, these data suggest that monotherapy with an AR antagonist is promising, and warrants further investigation. The recent availability of significantly more potent second generation inhibitors of the AR makes such a study even more compelling.

## 1.4 SECOND GENERATION AR ANTAGONISTS IN BCR HORMONE SENSITIVE PROSTATE CANCER

First generation AR antagonists such as flutamide and bicalutamide have relatively low AR binding affinity relative to dihydrotestosterone (DHT) and may exhibit partial agonist activity and may eventually lead to disease progression through putative activation of the AR. To overcome the potential deficiencies of first generation antiandrogens, second generation antiandrogens have been developed which potently inhibit AR activation, nuclear translocation, binding to co-activators, and AR-mediated gene expression. Furthermore, these second generation antiandrogens do not have any agonist activity. ARN-509 is a second generation antiandrogen currently being evaluated in men with a more advanced, potentially AR-amplified,

castrate-resistant disease state. ARN-509 demonstrates a higher affinity for the AR than first generation AR inhibitors such as bicalutamide (see figure 1 below) [30]. Furthermore, ARN-509 lacks agonist activity, and additionally, inhibits AR nuclear translocation and DNA binding to androgen response elements, thereby modulating AR-mediated gene expression that drives prostate cancer growth [30, 31].

**Figure 1. Competitive Binding Curve of AR in LNCaP/AR Cells**




ARN-509 binding affinity for AR was evaluated in a whole cell binding assay in which competitive inhibition of 18-FDHT (18-fluorodihydrotestosterone) equilibrium binding to AR in LNCaP/AR cells was monitored. ARN-509 is a potent, competitive binder of AR, with a mean IC50 of 16 nM. In comparison, IC50 value for bicalutamide was 160 nM.

ARN-509 was recently evaluated in a Phase 1/2 trial of men with metastatic castrate-resistant prostate cancer (CRPC) (NCT01171898). Thirty patients received ARN-509 at doses 30, 60, 90, 120, 180, 240, 300, 390, and 480 mg/day [32]. There was 1 dose-limiting toxicity (DLT) observed in the 300 mg/day cohort, a Grade 3 abdominal pain, which resolved upon study drug interruption and subsequent dose reduction. As a result of this DLT, an additional 3 patients were enrolled in the 300 mg/day cohort; there were no additional DLTs observed. The most commonly reported Grade 1-2 treatment-related adverse events were fatigue, abdominal pain, dyspnea, nausea, and arthralgia. Grade 1 or 2 hypothyroidism was also reported as a treatment-related adverse event. There were no Grade 4 or 5 adverse events observed. Pharmacokinetic (PK) studies demonstrated that ARN-509 was rapidly absorbed, with measurable plasma concentrations within 30 minutes after ingestion of a single oral dose of 30 to 480 mg. On average, peak plasma concentrations occurred 2 to 3 hours after administration in each dose cohort. The increases in plasma maximum concentration ($C_{max}$) and in the area under

the plasma concentration vs. time (AUC) were linear and dose proportional. Based on the clinical safety and pharmacokinetic profile observed, 240 mg/day was selected as the recommended Phase 2 dose of ARN-509 [32]. The Phase 2 portion of the study is ongoing to evaluate the safety and efficacy of ARN-509 in subjects with high-risk (PSADT ≤10 months or serum PSA value ≥8 ng/mL obtained within 3 months prior to enrollment) non-metastatic (CRPC) and subjects with mCRPC who had or had not received prior treatment with abiraterone acetate. The safety profile of ARN-509 in these patient populations is consistent with the Phase 1 data in patients with mCRPC.

Refer to the Investigator's Brochure for comprehensive information on the nonclinical and clinical data for ARN-509.

Given the fact that patients with hormone-sensitive BCR have AR dependent, yet likely non-AR amplified cancer, with a low tumor burden, potent blockade of the AR with a second generation antiandrogen may demonstrate significant cytotoxic effect and clinical efficacy.

## 1.5 DEMONSTRATING BENEFIT OF NOVEL HORMONE THERAPIES IN BCR PROSTATE CANCER PATIENTS

Developing new therapeutics and therapeutic strategies for men with BCR presents some unique study design challenges. The relatively long median metastasis-free and overall survival with ADT require trials enrolling large numbers of patients with long term follow up to demonstrate statistically non-inferior or superior progression-free or overall survival of a new treatment strategy pitted against continuous ADT. However, there exist a number of other clinically relevant and statistically rigorous endpoints, including quality of life and impact on metabolic parameters, which can be addressed in smaller randomized Phase 2 trials. In addition to addressing important clinical issues, favorable results from such trials can then provide the basis and justification to support larger clinical trials with primary efficacy endpoints of metastasis-free or overall survival.

### 1.5.1 Quality of Life

The potential side effects and adverse effect on quality of life with traditional ADT, coupled with an expected median overall survival of men with BCR on the order of 5 years or longer, even among those with a short PSADT, makes preservation of quality of life (QOL) an important goal for new therapeutics tested in the BCR disease population. There are several validated quality of life scales which have been used in prior prostate cancer clinical trials, including the Functional Assessment of Cancer Therapy- Prostate (FACT-P) [33], the EORTC QLQ-C30 plus EORTC QLQ-PR25 prostate cancer-specific subscale [34, 35], the UCLA Prostate Cancer Index (PCI) [36], the Expanded Prostate Cancer Index Composite (EPIC) [37], and the Sexual Health Inventory for Men (SHIM) [38]. For the current study proposal, FACT-P, EORTC QLQ-C30/QLQ-PR25, and the SHIM instruments will be used to measure various aspects of quality of life among men treated with hormonal therapy for biochemically relapsed prostate cancer.

#### 1.5.1.1 FACT-P

Although there is no QOL scale specifically designed and validated for use in the BCR disease population, perhaps the most widely used and validated QOL scale used in clinical trials of men with advanced prostate cancer is the FACT-P scale [33]. The FACT-P includes a 27-item "core"

quality of life measure (FACT-G), grouped into 4 sub-scales: physical, social/family, emotional, and functional well-being. The prostate cancer-specific subscale contains an additional 12 items, which address changes in weight, appetite, pain control, bowel/bladder function, and erectile dysfunction [see Appendix 1], which encompass many of the QOL issues expected with ADT.

#### 1.5.1.2 EORTC QLQ-C30/QLQ-PR25

The EORTC QLQ-C30is a well validated [34], and widely used measure of health-related quality of life among cancer patients. The EORTC QLQ-C30 consists of 30 items, which list the functioning and symptoms of cancer patients. Five multi-item function scales are scored: physical function (PF), role function(RF), emotional function (EF), social function (SF), and global health status/quality of life. Furthermore, nine single-item scales(symptoms) are scored, including fatigue, pain, dyspnea, and gastrointestinal problems. The QLQ-PR25 is a well validated [35] 25 item subscale specific to prostate cancer patients, including items specific to the use of ADT such as those pertaining to hot flushes, weight gain, fatigue, and libido [see Appendix 2].

#### 1.5.1.3 Sexual Health Inventory for Men (SHIM)

For men on ADT, one of the most impactful side effects on QOL is the potential for impotence and decrease in sexual function. The SHIM is a well validated [38] and widely used 5 item scale used to assess the severity of erectile dysfunction which has been included in prior prostate cancer studies [39].

### 1.5.2 Metabolic Parameters

#### 1.5.2.1 Markers of Insulin Resistance and Metabolic Syndrome

Androgen deprivation therapy has numerous effects on the metabolic profile, including increased insulin resistance, development of obesity and increased waist circumference, unfavorable changes in the lipid panel, and ultimately increased risk of diabetes and potentially cardiovascular mortality [15-21]. To detect differences in the incidence rate of new diabetes or cardiovascular events between treatment arms, studies in the BCR disease setting would require large numbers of patients and long term follow up, given the low annual incidence rate of these co-morbidities for men on ADT. Measuring changes in metabolic risk factors for these processes, including surrogate markers of insulin resistance such as fasting glucose and insulin, body mass index, hemoglobin A1C, along with changes in the fasting lipid panel, may serve as intermediate, exploratory endpoints in initial phase 2 trials. Favorable results with respect to these metabolic parameters may then serve as the basis for larger trials of new therapeutic agents, in which the incidence rate for diabetes or cardiovascular disease could serve as more quantifiable endpoints.

#### 1.5.2.2 Bone Mineral Density (BMD)

Bone mineral density, as measured by dual energy x-ray absorptiometry (DEXA) scan, remains the standard method of diagnosing osteoporosis and estimating osteoporotic fracture risk, defined as vertebral compression fractures or fractures after a fall from a standing height or less in the absence of other significant trauma. In general, for each standard deviation decrease in BMD by DEXA scan, the risk of osteoporotic fracture doubles [40]. Prior studies have shown that continuous treatment with ADT decreases BMD. For example, in a prior study of 65 men who

had proximal femur BMD measured at baseline and again after 12 months of ADT with LHRHa therapy, the mean BMD decreased by 1.9 ± 2.7% ($p < 0.001$) [41], demonstrating that even 1 year of ADT can adversely affect BMD. In addition, patients on ADT appear to be at increased risk for osteoporotic fracture. In a prior retrospective cohort study of the 50,613 men who were listed in the linked database of the Surveillance, Epidemiology, and End Results program and Medicare as having received a diagnosis of prostate cancer in the period from 1992 through 1997, of those men surviving at least 5 years after diagnosis, 19.4% of those receiving ADT sustained a fracture, compared with 12.6% of those not receiving ADT ($p< 0.001$) [42].

Measuring changes in BMD may serve as an intermediate, exploratory endpoint for a therapeutic agent tested in the BCR disease population. Favorable results with respect to better preservation of BMD over time compared to traditional ADT would then serve as the basis for larger trials with longer follow up using a more definitive endpoint such as incidence of osteoporotic fractures.

### 1.6 OVERALL STUDY RATIONALE

Prostate cancer patients with BCR, and a PSADT of 12 months or lower represent a subset of patients at significant risk for the development of metastases and prostate cancer-specific mortality. In general, ADT is an appropriate approach for these patients, but carries risks of its own, including a potential impact on QOL, and the potential for clinically significant metabolic derangements. Consequently, new strategies that can mitigate these adverse effects represent an important unmet need. Two potential strategies in this group of patients are a) to utilize a highly active second generation androgen receptor (AR) inhibitor as monotherapy and b) to add a highly active second generation AR inhibitor to conventional LHRHa IADT. The first approach is predicated on the expectation that AR inhibitor monotherapy will have fewer adverse events, while the second approach is based on the expectation that more effective combination therapy will result in greater anti-cancer activity, and consequently, after a finite period of therapy, allow a longer period of time off ADT (and hence improved QOL) as part of an intermittent ADT approach.

The proposed clinical trial will study the effects of 12 months of therapy with ARN-509 alone, or in combination with an LHRHa, each compared with LHRHa alone, in men with a rapidly rising serum PSA after prior definitive local therapy for prostate cancer. Endpoints selected reflect measurable short term effects of ADT, including quality of life and several metabolic parameters. In addition, the relative effect of each treatment strategy on PSA suppression as well as testosterone recovery (and subsequent PSA progression) after 12 months of therapy will be evaluated. Favorable results suggesting an improvement in QOL for either strategy will provide justification for larger definitive trials of second generation AR inhibitors as a treatment alternative or addition to LHRHa therapy in the BCR disease population.

# 2 HYPOTHESIS AND STUDY OBJECTIVES

## 2.1 HYPOTHESIS #1:

For men with non-metastatic, non-castrate prostate cancer who have rapidly rising PSA levels after definitive local therapy, treatment with 12 months of ARN-509 monotherapy compared with 12 months of ADT in the form of LHRHa monotherapy will result in better preservation of QOL as measured by the FACT-P scale. Parallel and exploratory findings demonstrating comparable PSA suppression, and less negative impact on the metabolic profile (including measurements of fasting lipid profiles, insulin resistance, and bone mineral density) of subjects who receive ARN-509 monotherapy as opposed to therapy with an LHRHa would form the preliminary basis for further definitive study of ARN-509 monotherapy in biochemically relapsed prostate cancer.

## 2.2 HYPOTHESIS #2:

For men with non-metastatic, non-castrate prostate cancer who have rapidly rising PSA levels after definitive local therapy, treatment with 12 months of therapy with the combination of ARN-509 + LHRHa, compared with 12 months of therapy with LHRHa alone, will not be associated with a clinically significant worsening of QOL as measured by the FACT-P scale. Parallel, exploratory findings suggesting more durable PSA suppression coupled with adequate serum testosterone recovery, favorable PSA modulation with respect to PSA nadir and time to PSA progression, along with acceptable safety data, would form the preliminary basis for larger clinical trials testing the combination of ARN-509 plus LHRHa vs. LHRHa alone in the hormone sensitive prostate cancer disease setting.

## 2.3 STUDY OBJECTIVES

### 2.3.1 Primary Objectives

- To compare the mean change from baseline in QOL as measured by total FACT-P score over a period of 12 months of therapy with ARN-509 monotherapy vs. LHRHa monotherapy in men with BCR to test for superiority with ARN-509 monotherapy.
- To compare the mean change from baseline in QOL as measured by total FACT-P score over a period of 12 months of therapy with ARN-509 + LHRHa vs. LHRHa monotherapy in men with BCR to test for non-inferiority with ARN-509 + LHRHa.

### 2.3.2 Secondary Objectives

- To compare (a) ARN-509 monotherapy vs. LHRHa monotherapy and (b) ARN-509 + LHRHa vs. LHRHa monotherapy with regards to change over time in QOL as measured by other QOL measurements.
- To compare (a) ARN-509 monotherapy vs. LHRHa monotherapy and (b) ARN-509 + LHRHa vs. LHRHa monotherapy with regards to PSA modulation.
- To compare (a) ARN-509 monotherapy vs. LHRHa monotherapy and (b) ARN-509 + LHRHa vs. LHRHa monotherapy with regards to metabolic and hormonal effects.

- To characterize the safety profile of ARN-509 monotherapy and in combination with LHRHa.
- Biomarker analyses will be conducted on formalin-fixed paraffin-embedded (FFPE) blocks or slides, plasma, and whole blood samples collected from consented subjects to assess $AR^{F876L}$ mutation and other resistance markers from all 3 treatment groups.

# 3 STUDY DESIGN

## 3.1 OVERALL STUDY CHARACTERISTICS

This is a Phase 2, randomized, open-label 3-arm multicenter study evaluating 12 months of treatment with an LHRHa monotherapy, ARN-509 monotherapy, or the combination in men with non-metastatic biochemically relapsed prostate cancer with rapidly increasing PSA levels after prior definitive therapy for localized prostate cancer. The two experimental arms (ARN-509 monotherapy; ARN-509 + LHRHa) will each be compared with a control arm of standard androgen deprivation (LHRHa monotherapy). Subjects will be stratified by PSADT (< 6 months vs. 6-12 months) and age (≤ 70 vs. greater than 70) and randomized with equal probability (1:1:1 ratio) from within each of the four strata to one of the 3 study arms.

There will be 2 treatment periods of 12 months each (24 months):

(1) On-therapy Period lasting 12 months, during which time subjects receive randomly assigned protocol therapy
(2) Off-therapy Observation Period from months 13 through 24

Subjects who develop progressive disease (either by serum PSA or radiographic progression) at any time during the 2 study periods will be removed from the study and will be treated as per individual investigator discretion. Subjects who discontinue before completion of the On-therapy Period in the absence of progressive disease will enter the Off-therapy Observation Period of the study. If subjects do not have evidence of PSA or radiographic progression at the end of 24 months, they will remain on study, enter a Follow-up Period, and be followed until PSA or radiographic progression or initiation of non-protocol therapy. Non-protocol therapy is defined as re-initiation of hormonal therapy or initiation of other anti-cancer therapy. The total study duration is 6 years from the date of first subject enrolled once the Off-therapy Observation Period has been completed. Subjects in the Follow-up Period will be discontinued at the time of the final clinical cutoff as described in Section 11.2.2.

## 3.2 STUDY ENDPOINTS

### 3.2.1 Primary Endpoint:

The mean change from baseline in total FACT-P score at 12 months

### 3.2.2 Secondary Endpoints:

*A) Quality of Life:*

- Mean change from baseline in total FACT-P score over time
- Mean change from baseline in EORTC QLQ-C30/PR25 score over time
- Mean change from baseline in SHIM score over time

*B) PSA Modulation:*

- Time to PSA progression. PSA progression will be defined as a rise to greater than 50% of the baseline serum PSA or rise of 2 ng/mL or more above the nadir, whichever is higher, confirmed by repeat measurement at least 2 weeks later.
- Proportion of subjects without evidence of PSA or radiographic progression during the 24-month treatment period and with recovery of serum testosterone at 24 months. Testosterone recovery will be defined as a serum testosterone > 150 ng/dL
- Proportion of subjects with a PSA less than 0.2 ng/mL after 7 months of protocol therapy

*C) Metabolic and Hormonal*

- Mean change from baseline in markers of insulin resistance (including body mass index, fasting glucose/insulin, and hemoglobin A1C), fasting lipid profile, and bone mineral density as measured at the femoral neck, and lumbar spine by DEXA scan over time
- For subjects randomized to the LHRHa-based treatment arms: the time to testosterone recovery to greater than 50 ng/dL (non-castrate) and > 150 ng/dL during the Off-therapy Observation Period
- The mean change from baseline in serum DHT and estradiol levels over time

*D) Safety:*

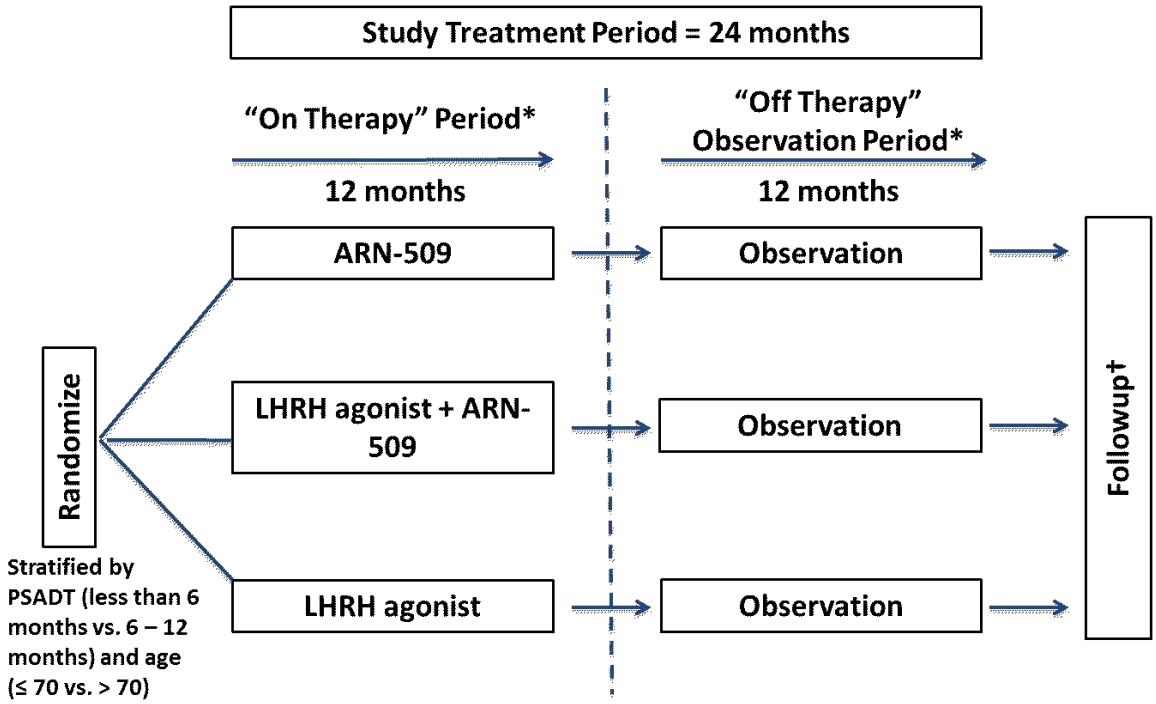
- Incidence and severity of adverse events.
- Abnormal findings in physical exams and laboratory tests

E) Correlative Studies

- Frequency of subjects emerging with $AR^{F876L}$ mutation at the end of treatment and progression.
- Frequency of subjects expressing various RNA markers previously demonstrated to confer resistance ARN-509 at baseline, end of treatment, and progression

### 3.3 STUDY SCHEMA

**N = 30 patients per arm**




*Patients with PSA or radiographic progression will discontinue protocol treatment and will be treated as per individual investigator discretion

† Patients will be followed until the time of PSA or radiographic progression, or initiation of non-protocol therapy, whichever happens first

### 3.4 STUDY TIMELINES

#### 3.4.1 Primary Completion:

With estimated accrual duration of 12 months, the data-cutoff for analysis of primary and secondary endpoints will be at 36 months from the time the study opens to accrual.

#### 3.4.2 Study Completion:

The study is estimated to reach completion 5 years from the time the study opens to accrual.

# 4 STUDY POPULATION

## 4.1 STUDY POPULATION

Ninety men, with a rising serum PSA after prior definitive therapy including radical prostatectomy or radiation therapy with curative intent, who have a PSADT ≤12 months, will be enrolled across multiple academic centers in the United States.

## 4.2 INCLUSION CRITERIA

1. Histologic confirmation of adenocarcinoma of the prostate
2. Rising PSA after prior definitive therapy for localized prostate cancer, including radical prostatectomy, external beam radiation therapy, brachytherapy, or combination of radical prostatectomy and radiotherapy
3. Prior primary or salvage radiation or not a candidate for localized salvage radiation due to subject preference or clinical assessment based upon disease characteristics and/or subject co-morbidities.
4. Minimum PSA:
    - 1.0 ng/mL if prior radical prostatectomy with or without adjuvant or salvage radiation
    - Nadir plus 2.0 ng/mL if prior definitive radiation therapy alone without prior radical prostatectomy
5. Criterion modified per amendment
    - 5.1 PSADT of less than or equal to 12 months:
        - PSADT calculation must include all recorded PSA values over the past 6 months prior to randomization, with a minimum of 3 values spaced at least 2 weeks apart, with each included value preferably measured at the same laboratory. PSA values obtained prior to localized therapy will be excluded.
        - The calculation of PSADT is based on the natural log of PSA.
        - Actual calculation of the PSADT can be obtained from the following online calculator: http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx
6. Criterion modified per amendment
    - 6.1 Criterion modified per amendment
    - 6.2 No evidence of metastatic disease on imaging by whole body bone scan and CT or MRI of the abdomen/pelvis within 6 weeks prior to randomization
        - Abdominal or pelvic lymph nodes measuring ≤2 cm in short axis are allowed.
7. Serum testosterone level ≥150 ng/dL
8. Criterion modified per amendment
    - 8.1 Criterion modified per amendment
    - 8.2 Prior ADT allowed if last dose was >6 months prior to randomization

9. Laboratory criteria include WBC > 3,000/mm³, hemoglobin > 7.0 g/dL, platelets > 70,000/mm³, total bilirubin < 2.0 mg/dL, AST less than 2.5 times the upper limit of normal
10. Criterion modified per amendment
    - 10.1 QTc ≤480 msec
11. Estimated life expectancy >5 years
12. ECOG performance status of 0 or 1
13. Criterion modified per amendment
    - 13.1 Age ≥18 years
14. Ability to sign written informed consent
15. Criterion modified per amendment
    - 15.1 Ability to swallow study drug whole as a tablet
16. Criterion modified per amendment
    - 16.1 Prior chemotherapy is allowed only in the (neo) adjuvant setting, and if last dose was >6 months prior to randomization
17. Criterion modified per amendment
    - 17.1 To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed while on study drug and for 3 months following the last dose of study drug.

### 4.3 EXCLUSION CRITERIA

1. Criterion modified per amendment
    - 1.1 Criterion modified per amendment
    - 1.2 Use of 5-alpha reductase antagonist (ie, finasteride, dutasteride) within 6 weeks prior to randomization
2. Criterion modified per amendment
    - 2.1 Criterion modified per amendment
    - 2.2 Use of antiandrogen (eg, flutamide, nilutamide, bicalutamide) within 6 weeks prior to randomization
3. Prior bilateral orchiectomy
4. Criterion modified per amendment
    - 4.1 Criterion modified per amendment
    - 4.2 Prior treatment with ADT for biochemically relapsed prostate cancer. Prior ADT as neo-adjuvant, concurrent, and/or adjuvant treatment following salvage radiation therapy or prostatectomy for biochemically relapsed disease is allowed provided last dose of ADT is >6 months prior to randomization and the screening serum testosterone level is ≥150 ng/dL.

5. Criterion modified per amendment
    - 5.1 Use of systemic steroids at an equivalent dose of prednisone 5 mg/day or higher at randomization
6. Criterion modified per amendment
    - 6.1 Use of other medications that are known to potentially lower serum PSA (ie, herbal medicines, nutritional supplements) within 6 weeks prior to randomization
7. Criterion modified per amendment
    - 7.1 Use of investigational agent within 6 weeks prior to randomization
8. Criterion modified per amendment
    - 8.1 Criterion modified per amendment
    - 8.2 Prior use of bone modifying agent(s) within 3 months prior to randomization
9. Any history of seizures or medical condition, which lowers seizure threshold
10. Prior pathologic findings consistent with small cell carcinoma, transitional cell carcinoma, or prostate cancer with neuroendocrine features

# 5 PROHIBITIONS AND RESTRICTIONS

During study treatment, the following prohibitions and restrictions apply:

If the subject is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies and their partners. Highly effective forms of contraception include:

- established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine (IUS) system;
- barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
- vasectomy;
- true abstinence (an option when this is in line with the preferred and usual lifestyle of the subject).

These restrictions must continue during treatment with study drug and for 3 months after the last dose of study drug.

# 6 STUDY RATIONALE

## 6.1 RATIONALE FOR THE STUDY POPULATION

Subjects with a PSADT of less than or equal to 12 months will be enrolled in an attempt to include as many subjects as possible while insuring that included subjects remain at sufficiently high risk to warrant ADT. Subjects will be stratified by PSADT of < 6 months vs. 6-12 months, as those with PSADT < 6 months have a shorter time to progression in prior studies [5]. Subjects will be additionally stratified by age (≤ 70 vs. > 70 at the time of study enrollment), as older age is associated with a longer time to testosterone recovery after cessation of ADT. The minimum PSA required for study entry follows commonly used guidelines to define biochemical recurrence while also allowing for accurate measurement of PSADT (greater than 1.0 ng/mL post-RP and nadir + 2 ng/mL post-RT) [43].

Prior ADT used in combination with RT will be permitted, as neoadjuvant, concurrent and adjuvant ADT is the standard of care for high-risk localized prostate cancer patients undergoing definitive radiation therapy. Prior ADT used in the context of RT will be permitted, provided the last effective ADT was > 6 months prior to randomization, and if serum testosterone has recovered to > 150 ng/dL prior to randomization. Due to relatively small sample size per study arm, PSADT and age will be the 2 stratification factors. Nevertheless, prior hormonal therapy will be a demographic variable compared between study arms. Time from definitive therapy to biochemical relapse, as well as Gleason grade at the time of diagnosis are 2 other validated prognostic factors in BCR patients, which will also be measured at baseline and compared between study arms [44, 45].

## 6.2 RATIONALE FOR TREATMENT ARMS

### 6.2.1 LHRHa Monotherapy as Control Arm

There is no universally accepted standard of care for patients with BCR and short PSADT. While randomized trials demonstrating an overall survival benefit of early vs. deferred ADT are lacking, treatment with an LHRHa is a commonly used practice. The decision to add a short course or prolonged treatment with a first generation antiandrogen such as bicalutamide to the LHRHa is quite variable across clinical practice, with no randomized data available to guide decision-making. In the metastatic setting, a first generation antiandrogen is often added concurrently or prior to initiation of ADT, to prevent a testosterone "flare" with initiation of ADT which can worsen pain and other symptoms from transient growth of cancer metastases. For this study population, with an absence of radiographically detectable metastases, this is less of a concern. Treatment with LHRHa monotherapy without a short course of a first generation antiandrogen is an acceptable treatment approach and will therefore be used as the shared control arm in this study. LHRH antagonists will not be permitted, as their relative efficacy in this setting is largely untested, and would introduce a potential confounder given the difference in rates of testosterone and PSA decline upon treatment initiation with this agent as compared with LHRH agonist therapy [46].

### 6.2.2 ARN-509 Monotherapy

Prior trials of monotherapy with a first generation AR inhibitor, bicalutamide, suggest that relative to LHRH therapy this approach may improve bone density, reduce the increase in fat

mass and diminish fatigue, loss of sexual interest and vasomotor flushing [29]. The question of whether 12 months of monotherapy with a highly potent, second generation, pure AR antagonist such as ARN-509, when compared with standard LHRHa therapy, can better preserve QOL, lessen impact on metabolic parameters such as fasting lipid profile, bone mineral density, and insulin resistance, while demonstrating comparable clinical efficacy with respect to changes in serum PSA has not previously been tested. In addition to preclinical data demonstrating the superiority of second generation AR antagonists, the clinical non-cross resistance of second generation AR antagonists with first generation AR antagonists provides a strong rationale to test these agents in this setting. Results from the proposed study, if favorable, would form the basis and justification for larger trials comparing ARN-509 monotherapy to ADT in BCR prostate cancer with both efficacy and safety/QOL endpoints.

### 6.2.3 ARN-509 + LHRHa

The combination of a second generation antiandrogen with an LHRHa has not previously been tested in BCR prostate cancer patients. The proposed study will test the hypothesis that the addition of ARN-509 to an LHRHa will not be associated with a clinically significant worsening of QOL compared with the LHRHa alone as measured by the FACT-P scale after 12 months of treatment. The addition of a highly potent, pure AR antagonist to standard LHRHa therapy will also generate preliminary data assessing whether treatment with the combination for a finite period of time (12 months), in a low tumor burden, non-AR amplified disease state, results in greater anti-cancer activity (as demonstrated by more durable PSA suppression), and consequently, allows a longer period of time off therapy. As discussed below, parallel, exploratory studies will compare the kinetics of testosterone recovery and PSA modulation. Findings suggesting adequate serum testosterone recovery, favorable PSA kinetics, along with acceptable QOL and safety data, would form the preliminary basis for larger clinical trials testing the combination of ARN-509 plus LHRHa vs. LHRHa alone.

## 6.3 RATIONALE FOR STUDY TREATMENT SCHEDULE

The study design utilizes the backbone of an intermittent therapy approach. Intermittent androgen deprivation therapy (IADT) has become an acceptable method of minimizing the toxicity of long term continuous ADT. IADT programs generally refer to “cycles” of treatment, with each cycle being comprised of an On -therapy Period followed by an Off-therapy Observation Period. In previously published IADT studies, in general, the initial induction On-therapy Period ranged between 8-12 months [47, 48]. The Off-therapy Observation Period is generally driven by PSA, with re-institution of ADT at a pre-determined PSA level. The first Off-therapy Observation Period can often equal or even exceed 12 months; however subsequent off-therapy intervals tend to become progressively shorter with each successive cycle of intermittent therapy [47-49]. Numerous Phase 2 and 3 trials comparing IADT to continuous ADT, though not adequately powered for non-inferiority, have shown comparable overall and prostate-cancer specific survival and improved QOL [22-25]. As discussed above, more recently, a randomized Phase 3, non-inferiority trial of continuous vs. intermittent ADT in 1,386 patients with BCR after prior definitive radiation treatment was conducted by the NCIC. There was no difference in overall survival after a median follow up of 6.9 years (HR = 1.02, 95% CI: 0.86, 1.21) and significantly better QOL with IADT [26]. The results of this trial provide further justification for the use of intermittent therapy in the trial design of the current study protocol.

The study plan for the proposed protocol consists of 2 periods. The first period is the On-therapy Period consisting of 12 months of randomly assigned protocol therapy to 1 of the 3 treatment arms. After 12 months of protocol therapy, if there is no evidence of PSA or radiographic progression, subjects will enter the Off-therapy Observation Period where they are followed by serial clinic visits and serum PSA and testosterone measurements without initiation of any subsequent therapy until the time of PSA or other progression. Data obtained from this clinical trial will form the basis of a larger, randomized Phase 3 trial that follows subjects through multiple periods of therapy.

## 6.4 RATIONALE FOR THE SELECTION OF STUDY EVALUATIONS

### 6.4.1 Primary Endpoint

The FACT-P scale has been chosen as the primary measure of QOL based on its prior validation and widespread use in clinical trials of men with advanced prostate cancer [33]. The generalized FACT-G scale together with the prostate cancer subscale contain items which encompass the clinical experience of men with prostate cancer, including general items addressing fatigue, side effects from therapy, physical function, emotional well-being, as well as those more specific to prostate cancer patients such as erectile dysfunction [see Appendix 1].

### 6.4.2 Secondary Endpoints

A number of additional endpoints will be evaluated to assess the overall impact of the assigned therapy. These endpoints fall under 3 categories: 1) further measures of QOL, 2) metabolic markers, including bone mineral density, and 3) PSA modulation and hormone levels.

#### 6.4.2.1 Other QOL Endpoints

Other QOL instruments will be administered and will be used to complement the FACT-P scale. The EORTC QLQ-C30, along with the prostate cancer subscale EORTC QLQ-PR25, are validated scales that have been used widely in prior trials of prostate cancer patients across a spectrum of disease stages [34, 35]. Specifically, the EORTC QLQ-PR25 contains multiple items pertaining to the use of ADT, including development of hot flushes, fatigue, weight gain, decreased libido, painful gynecomastia, and decreased sexual function [see Appendix 2], and thus can serve as a particularly useful measure of QOL during hormonal therapy for prostate cancer. Additionally, the SHIM scale will be used to assess sexual function, as erectile dysfunction can often be among the most troubling side effects of androgen deprivation therapy and therefore have a significant impact on QOL and tolerability of treatment [see Appendix 3].

#### 6.4.2.2 Metabolic Markers

Although the proposed study is not designed to detect differences in study arms in the incidence of diabetes, cardiovascular events, or osteoporotic fractures, risk factors for these conditions will be measured on a regular basis during protocol therapy. These include intermediate markers of insulin resistance, including fasting serum glucose and insulin, body mass index, and hemoglobin A1C, fasting lipid panel, as well as bone mineral density as measured by DEXA scan.

#### 6.4.2.3 PSA Modulation and Hormone Levels

The extent to which a therapeutic intervention modulates PSA levels has not been extensively evaluated as an intermediate marker of outcome in patients with BCR prostate cancer. In the proposed trial, three different aspects of PSA modulation will be evaluated: PSA nadir level, time to PSA progression, and PSA non-progression in the face of normal testosterone levels. In addition, the effect of the therapeutic interventions on relevant hormonal levels such as testosterone, DHT and estradiol will be evaluated.

PSA Nadir: In a prior clinical trial of men with metastatic hormone sensitive prostate cancer, after 7 months of induction ADT, men with a nadir PSA level of less than 0.2 ng/mL vs. 0.2 thru 4.0 vs. > 4.0 had a progressively shorter overall survival, declining from a median of 75 to 44 to 13 months, respectively [52]. Further, recommendations for trial design in BCR disease by the PSA Working Group [50] suggest that PSA decline can form the basis for larger trials using primary endpoints such as metastasis-free or overall survival. Whether the PSA nadir data observed in patients with metastatic disease is relevant to patients with BCR is not known. Nevertheless, as an exploratory secondary endpoint, the proportion of men achieving a PSA nadir after 7 months of protocol therapy of less than 0.2 ng/mL will be measured in the proposed trial. Validation of nadir PSA as a potential intermediate endpoint of metastasis-free or overall survival, however, will require confirmation in large prospective trials in this disease setting.

Time to PSA Progression: There is no consensus or standardized definition of PSA progression in the BCR disease setting. Various PSA thresholds have been used as a "trigger" to initiate treatment in prior trials of IADT, ranging from < 1.0 ng/mL to 20 ng/mL [47]. The recently reported NCIC-PR7 international trial of continuous vs. intermittent ADT used a PSA threshold of 10 ng/mL to restart ADT in the intermittent treatment arm [26], although this relatively high PSA value would be unlikely to be accepted by patients in the United States, who are accustomed to taking action based on much lower PSA values.

The PSA Working Group guidelines suggest that the mechanism of the investigative agent be taken into account when setting a PSA level to define recurrence [50]. For example, the addition of a cytotoxic chemotherapeutic agent to hormonal therapy, in which the treatment goal is to eradicate residual disease and achieve long term remission, any detectable PSA might be an appropriate level to define disease recurrence. For hormonal therapy, particularly when intermittent therapy is being considered, efforts have been made to individualize the PSA at which therapy is re-initiated, in order to reflect the fact that there is a broad range of baseline PSA values at which patients are first treated. Thus, in some IADT series, PSA recurrence has been defined as a rise in serum PSA to more than 50% of baseline level [51]. In patients previously treated with RT, progression has been defined as a serum PSA increase to greater than 2 ng/mL above the serum PSA nadir, reflecting the ASTRO guidelines for defining biochemical recurrence after prior definitive RT for localized prostate cancer [43].

For the purposes of this study, PSA progression during either the On-therapy Period or Off-therapy Observation Period will be arbitrarily defined as an increase in serum PSA to 50% or greater compared with baseline, or an absolute increase in 2 ng/mL or more above the nadir, whichever is higher, confirmed by repeat serum PSA measurement at least 2 weeks later. This definition in part draws on ASTRO guidelines defining biochemical recurrence after prior definitive radiation therapy, and in part reflects current clinical practice in which the patient's

baseline serum PSA level prior to starting treatment is taken into account when making treatment decisions regarding the re-initiation of therapy during the observational phase of IADT. The definition of PSA progression in the proposed trial, as in all trials of IADT to date, is arbitrary, but will be uniformly applied to all enrolled patients.

The PSA working group has suggested that duration of clinical activity is a key intermediate endpoint in initial Phase 2 trials of agents conducted in the BCR disease population [50]. Indeed, in an exploratory analysis of a trial of IADT in BCR patients, Yu and colleagues demonstrated that in patients who completed the first cycle of IADT, a shorter duration of the first "off treatment" interval was associated with a shorter time to developing castrate resistant prostate cancer and shorter overall survival [53]. In the proposed trial, the time to PSA progression from the initiation of protocol therapy (ie, Day 1 of On-therapy Period) will be evaluated for each of the 3 treatment arms. This analysis is exploratory in nature, both because the definition of "PSA progression" and the consequent resumption of therapy on an intermittent program is arbitrary, and because this endpoint requires a sufficient number of patients and duration of follow-up to record enough PSA progression events to have adequate statistical power to detect a difference between study arms. Nevertheless, data suggesting that the time to PSA progression was similar with ARN-509 monotherapy or with LHRHa monotherapy, or alternatively, suggesting a longer time to PSA progression when ARN-509 was added to LHRHa monotherapy would be provocative, and serve as the potential basis for launching a more definitive Phase 3 trial.

PSA Suppression with Normal Testosterone Levels: In BCR prostate cancer patients, minimizing toxicity while preserving clinical efficacy is a central goal of treatment. Much of the toxicity of ADT results from its induction of a hypogonadal state. Treatment alternatives to continuous ADT, such as IADT, seek to minimize decrements in quality of life and metabolic parameters induced by medical castration by increasing the percentage of time that patients spend in a eugonadal state. Thus, preservation of, or a return to, normal testosterone level, while maintaining a durable effect on serum PSA, is a potentially clinically relevant endpoint that could be measured utilizing the proposed study design, which incorporates intermittent therapy. In the proposed trial, this is an exploratory endpoint, since cessation of therapy does not necessarily equate to a return to eugonadal state, and there is a considerable variability in the time to serum testosterone recovery in prior studies of short-term ADT or IADT. For example, in a randomized trial of IADT with 6 months of induction ADT followed by randomization to either thalidomide vs. placebo, Gulley and colleagues demonstrated that the median time to low testosterone (defined as > 50, but < 212 ng/dL) or normal testosterone (defined as > 212 ng/dL) recovery was 12.9 and 16.6 weeks, respectively [54]. However, there was considerable variability with some patients taking up to 40 weeks to achieve a testosterone level > 50 ng/dL. Advanced age and low baseline serum testosterone level (< 212 ng/dL) were associated with a delay in time to testosterone recovery in this study. Twenty percent of men older than 66 years did not achieve normal testosterone levels by 44 weeks after cessation of ADT. In another report by Pickles and colleagues, in 267 patients treated with ADT for 3 months to 3 years in duration, the median time to testosterone recovery after cessation of ADT (defined as testosterone > 10 nmol/L or 288 ng/dL) was approximately 10 months [55]. Again there was considerable variability in the time to recovery; both older age and low baseline serum testosterone were associated with a longer time to testosterone recovery. Despite these limitations, assessment of serum testosterone recovery is an important parameter to be measured in studies of BCR men

receiving novel treatments or treatment strategies that incorporate ADT into the study treatment plan.

Thus, in the proposed study, the proportion of subjects who completed 24 months (12 months of treatment followed by 12 months of observation) and who have recovered serum testosterone to > 150 ng/dL while remaining PSA progression and metastasis-free will be calculated as an exploratory secondary endpoint. Using a cutoff of serum testosterone greater than 150 ng/dL is acknowledged to be somewhat arbitrary, as prior clinical studies measuring the time to testosterone recovery have used a range of serum testosterone thresholds ranging from 150-300 ng/dL. Nevertheless, treatment strategies that achieve durable PSA suppression with a finite period of treatment, while either avoiding castration altogether or allowing serum testosterone recovery during Off-therapy Observation Period, would be worthy of further investigation in Phase 3 trials.

Hormone Levels: The androgen receptor is activated by various androgenic ligands besides testosterone, including dihydrotestosterone (DHT), which is produced from testosterone by the enzyme 5-alpha reductase. In hormone-sensitive prostate cancer patients treated with traditional ADT, serum levels of DHT decrease with treatment. For example, in a prior study of 69 patients treated with ADT for a period of 6 months, serum DHT levels decreased by an average of 92.5% compared with pretreatment serum levels [56]. Furthermore, bicalutamide monotherapy increases serum concentrations of testosterone and estradiol [29]. Because estradiol plays an important role in skeletal homeostasis in normal men, this may be the mechanism by which bicalutamide monotherapy lacks the adverse skeletal effects of LHRHa. A significant caveat, however, is that serum androgen levels may not reflect tissue hormone levels. Indeed, in the previously mentioned study above, though serum DHT levels decreased by 93% after 6 months of ADT, tissue DHT levels decreased by only 75%, and there was only a weak correlation between serum and tissue DHT levels ($r = 0.229$; $p = 0.025$) [57]. Nevertheless, the ready availability of serum hormone levels and their potential utility as intermediate outcome markers warrants their assessment in an exploratory fashion.

In summary, the proposed trial will evaluate the effects of 12 months of therapy with a highly potent AR inhibitor (ARN-509) alone, or in combination with an LHRHa, each compared with LHRHa alone on a number of short-term markers, including quality of life, metabolic parameters, and PSA modulation. The anticipated results from this trial may provide justification for larger definitive trials of second generation AR inhibitors as a treatment alternative to LHRHa monotherapy in patients with BCR.

#### 6.4.2.4 Correlative studies: Exploratory Biomarkers:

- For consenting subjects, archived tumor samples FFPE blocks or slides will be collected any time after enrollment to gain understanding of biology and identify markers associated with response or resistance to complete androgen annihilation compared with apalutamide or LHRH alone

- For consenting subjects whole blood will be collected at baseline (predose on Day 1 of study treatment) and end of treatment or progression in PAXgene tubes for RNA testing for markers previously demonstrated to confer resistance to ARN-509 (see Section 7.1).

These include androgen receptor anomalies (eg: AR amplification, ARv3/7, and ARv567), AR axis genes, and other compensatory pathway markers.

- Previous studies with metastatic CPRC subjects provide evidence that an acquired mutation in the androgen receptor ($AR^{F876L}$) may be associated with resistance to ARN-509 treatment [60]. Plasma-based circulating DNA will be used to assess the presence of the $AR^{F876L}$ mutation at progression

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# 7 STUDY ACTIVITIES

## 7.1 STUDY SCHEDULE: ON- THERAPY PERIOD (DAY 1 – MONTH 12)

| | Pre-Study[1] | Day 1[1] | Therapy | End of each month[2,5] | End of Month 3[3,5] | End of Month 6[3,5] | End of Month 9[3,5] | End of Month 12[3,5] | Progression Visit (PSA or radiographic) (if before End of Month 12)[4] |
|---|---|---|---|---|---|---|---|---|---|
| LHRH agonist (in 2 of the 3 treatment arms) | | X[5] | X[5] | | | | | | |
| ARN-509 (in 2 of the 3 treatment arms) | | X[5] | X[5] | | | | | | |
| Informed Consent | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| History/Physical Exam[6] | X | X | | X | | | | | X |
| Safety Assessment[7] | X[7] | X | | X | | | | | X |
| Concomitant Medications | | | | X[8] | | | | | |
| Height | X | | | | | | | | |
| Weight/BMI | X | X | | X | | | | | |
| ECOG Performance Status | X | | | X | | | | | X |
| CT or MRI of abd/pelvis | X[9] | | | | | | | | X[9] |
| Whole body bone scan | X[9] | | | | | | | | X[9] |
| FACT-P, EORTC QLQ-C30/QLQ-PR25, SHIM | X | | | | X | | | X | X[10] |
| DEXA scan (BMD measured at femoral neck and lumbar spine)[11] | X[12] | | | | | | | X | X[12] |
| Electrocardiogram | X | | | | | | | | |
| CBC w/diff and platelets | X | | | | X | X | X | X | X |
| ALT, AST, AlkP, total bilirubin | X | | | | X | X | X | X | X |
| TSH | X | | | | X | X | X | X | X |
| PSA[13] | X | X | | X | | | | | X |
| Fasting glucose, lipids, HgbA1C | X | | | | X | X | X | X | X |
| Serum testosterone, Estradiol, DHT, and fasting insulin[14] | X | | | | X | X | X | X | X |
| Plasma/Serum/Urine for banking (optional)[15] | | X | | | X | X | X | X | X |
| PBMCs for banking (optional)[15] | | X | | | | | | | |
| Whole blood RNA testing (optional)[16] | | X | | | | | | X | X |

| | Pre-Study[1] | Day 1[1] | Therapy | End of each month[2,5] | End of Month 3[3,5] | End of Month 6[3,5] | End of Month 9[3,5] | End of Month 12[3,5] | Progression Visit (PSA or radiographic) (if before End of Month 12)[4] |
|---|---|---|---|---|---|---|---|---|---|
| Plasma for biomarker testing (optional)[17] | | | | | | | | X | X |
| Archival FFPE tumor blocks or slides for biomarker assessments (optional) | | X[18] | | | | | | | |

abd = abdomen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AlkP = alkaline phosphatase;; BMD = bone mineral density; BMI = body mass index; CBC = complete blood count; CT = computed tomography; DEXA = dual energy x-ray absorptiometry; DHT = dihydrotestosterone; ECOG = Eastern Cooperative Oncology Group; eCRF=electronic case report form; EORTC = European Organization for Research and Treatment of Cancer; FACT-P = Functional Assessment of Cancer Therapy-Prostate scale; FFPE=formalin-fixed paraffin-embedded; HgbA1C = hemoglobin A1C; ICF = informed consent form; LHRHa = luteinizing hormone releasing hormone agonist; MRI = magnetic resonance imaging; PBMCs = peripheral blood mononuclear cells; PSA = prostate-specific antigen; SHIM = Sexual Health Inventory of Men Index; TSH=thyroid stimulating hormone;

[1]Pre-study assessments need to be completed within 14 days prior to randomization. Day 1 must occur within 5 calendar days of randomization.
[2]Subjects who discontinue during the On-therapy Period in the absence of progressive disease will enter the Off-therapy Observation Period of the study (see schedule below). If at any time a subject initiates a non-protocol therapy, the subject will be removed from study and treated as per individual investigator discretion.
[3] In addition to the end of each month visit assessments. Window for all visits is during treatment is ±2 days. Window for laboratory assessments before study visits is -7 days.
[4] Complete these assessments if a subject develops PSA or radiographic progression before the end of Month 12. The subject will then be removed from study and treated as per individual investigator discretion
[5] Choice of LHRHa is per investigator's discretion. The first dose of ARN-509 or LHRHa will be on Day 1. ARN-509 will be administered daily with or without food. All subjects should be following a 28-day, 28-day, 35-day schedule for their monthly visit (i.e., the 1st post-Day 1 visit is scheduled for 28 days later, the 2nd post-Day 1 visit is scheduled for 28+28 days later, the 3rd post-Day 1 visit is scheduled for 28+28+35 days later, the 4th post-Day 1 visit is scheduled for 28+28+35+28 days later, etc). If a subject does not receive a scheduled LHRHa injection within ±7 days of the scheduled due date for injection, he will be removed from study
[6] Physical exam changes will not be collected in the eCRF, any change in physical exam from baseline needs to be recorded on the adverse event page
[7] Adverse event collection starts from signing the ICF. For subjects who discontinue therapy and do not proceed to the Off-therapy Period, AEs must be recorded up to 30 days after the last dose of study medication.
[8] See Section 7.5.4.
[9] Scans need to be done within 6 weeks prior to randomization. At the Progression Visit, scans may be omitted if already done within the prior 1 month.
[10] At the Progression Visit, may be omitted if already done with the prior 1 month.
[11] For reference, see, https://www.shef.ac.uk/FRAX/tool.aspx?country=9. DEXA scan is also to be used for osteoporosis assessment.
[12] DEXA scan needs to be done within 12 weeks prior to randomization. At Progression Visit, scans may be omitted if already done within the prior 1 month.
[13] PSA laboratory evaluations should preferably be performed by the same laboratory using an ultrasensitive assay. Serum PSA sample on Day 1 should be taken predose.

[14] See Appendix 6 for details on collection, processing, and shipping of peripheral blood samples collected for measurement of testosterone, DHT, estradiol, and fasting insulin.
[15] The banking of plasma, serum, urine, and PBMCs is optional (see Appendix 6 for collection, processing, and shipping instructions). Samples should be collected predose on Day 1.
[16] Whole blood to be collected in PAXgene tubes (2.5 ml) (optional) (see Appendix 6 for collection, processing, and shipping instructions). Samples should be collected predose on Day 1.
[17] Plasma to be collected in EDTA tubes (10 mL) (optional) (see Appendix 6 for collection, processing, and shipping instructions).
[18]The FFPE tumor blocks or slides may be collected anytime during or after enrollment.

## 7.2 STUDY SCHEDULE: OFF-THERAPY OBSERVATION PERIOD (MONTHS 13-24) AND FOLLOW-UP PERIOD (MONTH 25+)

| | End of every 2 months | End of Month 18[2] | End of Month 24[2] | Progression Visit (PSA or radiographic) (if occurs before End of Month 24) | Follow-up Period (Month 25+)[3] |
|---|---|---|---|---|---|
| History/Physical Exam[1] | X | | | X | X |
| Safety Assessment | X | | | X | |
| Weight/BMI | X | | | | |
| CT or MRI abd/pelvis | | | | X | |
| Whole body bone scan | | | | X | |
| FACT-P, EORTC QLQ-C30/PR25, SHIM | | | X | X[6] | |
| PSA[4] | X | | | X | X |
| Serum testosterone[5] | X | | | X | X |
| Fasting glucose, lipids, serum insulin[5], HbA1C | | X | X | X | |
| Whole blood RNA testing (optional)[5] | | | | X | X[7] |
| Plasma for biomarker testing (optional)[5] | | | | X | X[7] |

abd = abdomen; BMI = body mass index; CT = computed tomography; eCRF=electronic case report form; EORTC = European Organization for Research and Treatment of Cancer; FACT-P = Functional Assessment of Cancer Therapy-Prostate scale; HgbA1C = hemoglobin A1C; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; SHIM = Sexual Health Inventory of Men Index

[1] Physical exam changes will not be collected in eCRF, any change in physical exam from baseline needs to be recorded on the adverse event page.
[2] In addition to the end of every 2-month visit assessments, visit window is ±7 days.
[3] Visit to occur every 3 months (±7 days). Subjects who develop PSA or radiographic progression, or initiate non-protocol therapy will be removed from study and treated as per individual investigator discretion.
[4] Preferably measured at the same laboratory using an ultrasensitive assay.
[5] See Appendix 6 for details on collection, processing, and shipping of peripheral blood for measurement of testosterone, fasting insulin, plasma DNA, and whole blood for RNA testing.
[6] May be omitted if already done within the prior 1 month.
[7] If no progressive disease occurred during Month 1-24, whole blood RNA and plasma for biomarker testing only need to be collected during the Follow-up Period when progressive disease occurs. (see Appendix 6 for collection, processing and shipping instructions).

## 7.3 SCREENING PERIOD/PRE-STUDY EVALUATION

All subjects must sign a written informed consent form before study specific-screening procedures are performed. Screening procedures to evaluate subject eligibility will be conducted within 14 days prior to randomization. The measurements collected at screening will be considered the baseline values except for PSA. Serum PSA measurements at Day 1 will be considered as baseline for PSA endpoints.

### 7.3.1 Clinical Assessments

- Complete history and physical examination
- Baseline demographics
- Height, weight, body mass index
- ECOG Performance Status (see Appendix **4**)
- FACT-P (see Appendix 1), EORTC QLQ-C30/EORTC QLQ-PR25 (see Appendix 2), and Sexual Health Inventory for Men (SHIM) (see Appendix 3)
- Electrocardiogram

### 7.3.2 Laboratory Assessments

- Complete blood count including differential and platelet count
- Total bilirubin, alkaline phosphatase, AST, ALT
- Thyroid stimulating hormone (TSH)
- Serum PSA level measured by ultrasensitive assay
- Calculation of PSA doubling time, using all known PSA levels within the past 6 months including screening PSA level (but not Day 1 PSA). There must be a minimum of 3 values spaced at a minimum of 2 weeks apart, with each included value measured at the same laboratory (preferably). PSA values obtained prior to localized therapy will be excluded. The PSA doubling time can be calculated from the website: http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx
- Fasting glucose, fasting lipid panel (total cholesterol, LDL, HDL, triglyceride), and hemoglobin A1C
- Peripheral blood collection for measurement of serum testosterone, DHT, estradiol, and fasting serum insulin levels (see Appendix 6 for collection, processing, and shipping instructions).

### 7.3.3 Radiographic Studies

Once the subject has given written informed consent and is eligible for the study as per the laboratory/clinical parameters outlined above, the following radiographic information will be collected.

- Radionuclide bone scan

- Cross-sectional imaging of the abdomen and pelvis with IV contrast per investigator discretion (CT or MRI). Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast or without any contrast, as long as method is identical each time new scans are done.
- DEXA bone densitometry scan with measured bone mineral density at the femoral neck, and lumbar spine (see https://www.shef.ac.uk/FRAX/tool.aspx?country=9).

Radionuclide bone scans and CT/MRI images must have been done within 6 weeks prior to randomization. There will be no central reading of the scans and radiographic progression is based on investigator assessment. The DEXA bone densitometry scan must have been taken within 12 weeks prior to randomization.

### 7.4 RANDOMIZATION:

Once eligibility is confirmed, subjects will be stratified according to their pre-study PSADT (<6 months vs. 6 – 12 months) and age at study entry (≤ 70 vs. > 70). They will be randomized with equal probability to 1 of the 3 treatment arms from within each of the 4 strata. Balance in treatment assignment will be achieved using a randomized block design. Randomization will be carried out via computer generated random assignment. All subjects must commence treatment within (5 calendar days) of randomization. Study sites will email the Eligibility Checklist to the sponsor in order to obtain the subject's treatment assignment. Once subject eligibility is confirmed by the sponsor, an email with the treatment assignment number will be provided to the study site.

### 7.5 STUDY PERIOD I: ON-THERAPY PERIOD (MONTHS 1 TO 12)

The 24-month study treatment period will be divided into two 12-month periods: the On-therapy Period during which subjects receive protocol therapy (ARN-509 monotherapy, ARN-509 + LHRHa, or LHRHa monotherapy). Subjects will commence protocol therapy on Day 1 of the On-therapy Period. The study timeline is defined as Day 1 = first dose of study treatment. Subsequent study time points will be defined based on study calendar, irrespective of subsequent dose delays/interruptions (see Section 9 for discussion of dose delays due to toxicity).

Subjects will be treated with protocol therapy for 12 months, or until disease progression (either by PSA or radiographic), unacceptable toxicity, subject/physician withdrawal, or initiation of non-protocol therapy. PSA progression is defined as an increase in PSA to > 50% of the baseline value or an increase of > 2 ng/mL above the nadir, whichever is higher confirmed by repeat measurement at least 2 weeks later. Radiographic progression is defined as the detection of new metastasis on either bone scan or cross-sectional imaging (CT or MRI) [61]. If subjects develop progressive disease (either by PSA or radiographic) while receiving protocol therapy, they will discontinue protocol therapy, have a Progression Visit, and be treated as per individual investigator discretion.

If there is no evidence of disease progression (by serum PSA or radiographically) after 12 months of protocol therapy or if subject discontinues treatment before 12 months of protocol therapy for reasons other than disease progression, subjects will enter the 12-month Off-therapy Observation Period. Continuation of hormone therapy or initiation of any form of anti-cancer

therapy in the absence of PSA or radiographic progression will be considered non-protocol therapy and will result in study removal.

Efforts will be made to ensure that subjects who develop progressive disease before 12 months of therapy still complete QOL scales at 3 and 12 months.

### 7.5.1 Day 1 of Study Treatment

Subjects will return to study site for a history and physical exam including weight, measurement of serum PSA, and dispensing of study drug(s), including the first injection of LHRHa and 1 month supply of ARN-509 for subjects randomized to those arms. Collection of optional samples (samples for banking, archival FFPE blocks or slides for transcriptome profiling (RNAseq), whole blood for RNA testing, and plasma for biomarker testing) should occur before predose.

### 7.5.2 LHRH Agonist

For subjects randomized to either the LHRHa monotherapy or the LHRHa + ARN-509 combination treatment arms, the choice and schedule of LHRHa will be up to individual investigator's discretion and will be administered for a total of 12 months of therapy in the absence of disease progression or unacceptable toxicity. No change in dosing schedule of LHRHa will be permitted once the subject has commenced protocol therapy. For example, the use of an every 3 month subcutaneously injected LHRHa would be administered on Day 1 and on Months 3, 6, and 9. The use of LHRH antagonists (ie, degarelix) will not be permitted as outlined in Section 6.2.1. No dose reductions or interruptions of LHRHa will be permitted (see Section 9.3). If a subject does not receive a scheduled LHRHa injection within ±7 days of the scheduled due date for injection, he will be removed from study. Subjects on the LHRHa monotherapy arm will not be allowed to crossover to receive ARN-509.

### 7.5.3 ARN-509

Subjects randomized to either of the two ARN-509-containing arms will receive ARN-509 dosed orally on a daily basis with or without food. The starting dose of ARN-509 is 240 mg/day. With Amendment 7 (Version 8.0), subjects who are receiving the softgel capsules will switch to the tablet formulation. Ongoing subjects on a reduced dose of capsules should continue with that dose with lowest allowed dose being 120 mg (see Section 8). Dose delays and dose reductions will be permitted as per guidelines outlined in Section 9.2.

### 7.5.4 Concomitant Medications

Concomitant medications will be recorded at each monthly clinic visit. Subjects are recommended to take calcium 1000 mg/day and vitamin D (cholecalciferol) 800 IU/day in divided doses. Phosphodiesterase inhibitors such as sildenafil used to treat erectile dysfunction may be initiated or continued as per individual investigator discretion. Breast irradiation and/or tamoxifen to prevent and/or treat painful gynecomastia will also be permitted per individual investigator discretion. Subjects who require the initiation of bisphosphonate or other bone-targeted therapy (eg, those sustaining an osteoporotic fracture) while on study will be permitted to do so and remain on study, but subjects who have used a bone-modifying agent within 3 months prior to randomization will be excluded (see Section 4).

#### 7.5.4.1 Prohibited Medications

No concomitant use of any anti-cancer therapy will be permitted. This will include surgery, radiation therapy, and other secondary hormonal therapies including first generation antiandrogens, 5-alpha reductase inhibitors (i.e. finasteride, dutasteride), megestrol acetate, immunotherapy, chemotherapy, or other investigational agents while on study [see Appendix **5** for list of prohibited treatments while on study]. Start of any of these therapies will result in discontinuation from the study, see Section 7.8. Nutritional supplements containing saw palmetto or pomegranate are also specifically prohibited.

#### 7.5.4.2 ARN-509: Prohibited Medications:

As a class effect, androgen receptor antagonists have been associated with seizures due to an off-target mechanism of action ($GABA_A$ inhibition). To date, no subjects receiving ARN-509 have experienced seizures, however, in preclinical experiments, at very high doses, dogs treated with ARN-509 had tremors and generalized seizures. Subjects will be closely monitored for seizures, but as a precautionary measure, the following drugs known to decrease the seizure threshold or cause seizure will be prohibited.

- Aminophylline, theophylline
- Atypical anti-psychotic drugs: clozapine, olanzapine, ziprasidone, bupropion
- Phenothiazine anti-psychotic drugs: chlorpromazine, mesoridazine, thioridazine
- Tricyclic and tetracyclic anti-depressants: amitriptyline, desipramine, doxipine, imipramine, maprotiline, mirtazapine (Remeron)
- Lithium
- Meperidine (Demerol) and pethidine

#### 7.5.4.3 ARN-509: Restricted Medications:

If it is absolutely necessary for the well-being of the subject and alternative therapies are not available, these drugs should be used with caution and after discussion with Dr. Aggarwal and the Sponsor's Medical Monitor. The list of medications that are prohibited or restricted while taking ARN-509, is provided in Appendix 5.

### 7.5.5 Safety Assessment

Subjects will be assessed for adverse events at each monthly clinic visit during the On-therapy Period. Adverse event collection starts with the signing of the ICF (see Section 7.1). Adverse events will be graded according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (available at http://ctep.cancer.gov). See Section 12.1.4 for attribution of adverse events. Dose modifications (interruptions, reductions or both) for ARN-509, will be allowed as per guidelines outlined in Section 9.2.

### 7.5.6 QOL

The FACT-P, EORTC QLQ-C30/QLQ-PR25, and SHIM questionnaires will be completed at the end of Month 3 and Month 12 or at the time of PSA or radiographic progression (if occurs before Month 12, every effort will be made to obtain the 12-month questionnaires for those who discontinue before 12 months).

### 7.5.7 Laboratory Assessments

Subjects who experience disease progression (PSA or radiographically) before the end of 12 months should complete laboratory assessments at the Progression Visit as outlined in the Study Schedule. During treatment, laboratory assessments include the following:

- Serum PSA level measured by ultrasensitive assay at the end of each month
- Complete blood count including differential and platelet count at the end of Months 3, 6, 9, and 12 of protocol therapy.
- Total bilirubin, alkaline phosphatase, AST, ALT at the end of Months 3, 6, 9, and 12.
- TSH at the end of Months 3, 6, 9, and 12.
- Fasting glucose, fasting lipid panel (total cholesterol, LDL, HDL, triglyceride), and hemoglobin A1C at the end of Months 3, 6, 9, and 12.
- Peripheral blood collection for measurement of serum testosterone, DHT, estradiol, and fasting serum insulin levels at the end of Months 3, 6, 9, and 12 ( see Appendix **6** for collection, processing, and shipping instructions).
- Peripheral blood and urine collection for banking of, serum, plasma, and urine at the end of Months 3, 6, 9, and 12 of protocol therapy (optional). See Appendix **6** for procedures to ensure subject confidentiality and instructions on collection, processing, shipping of samples.
- Whole blood collected for PAXgene analysis (optional) on Day 1 and end of Month 12

### 7.5.8 Radiographic Assessments

A whole body nuclear bone scan, along with cross-sectional imaging of the abdomen/pelvis (CT or MRI) will be obtained as prompted by signs and symptoms of metastatic disease and at the time of PSA progression. DEXA scan measuring BMD at the femoral neck, and lumbar spine will be obtained after 12 months of protocol therapy or at the time of PSA or radiographic progression (if occurs before Month 12, see Progression Visit in Study Schedule).

Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast or without, as long as method is identical each time new scans are done.

There will be no central reading of the scans and radiographic progression will be based upon investigator assessment.

## 7.6 STUDY PERIOD II: OFF-THERAPY OBSERVATION PERIOD (MONTHS 13 TO 24)

Subjects without progressive disease (by PSA or radiographic) after 12 months of protocol therapy will stop protocol therapy and enter the Off-therapy Observation Period from Month 13 to Month 24. Continuation of hormonal therapy or initiation of any other of anti-cancer therapy in the absence of PSA or radiographic progression will be considered non-protocol therapy and will result in study removal. Use of concomitant medications, which may affect serum PSA will not be permitted (see Section 7.5.4).

Subjects who develop either PSA or radiographic progression during the Off-therapy Observation Period will have a Progression Visit, and be treated as per individual investigator discretion. Efforts will be made to ensure that subjects who develop progressive disease (PSA or radiographic) or discontinue in the absence of progressive disease before 24 months still complete QOL scales after 24 months as prespecified in the study protocol.

### 7.6.1 Safety Assessment

Subjects will be assessed for adverse events at clinic visits at the end of every 2 months during the Off-therapy Observation Period.

### 7.6.2 QOL

The FACT-P, EORTC QLQ-C30/QLQ-PR25, and SHIM questionnaires will be completed at the time of progression (PSA or radiographic) or after 24 months.

### 7.6.3 Laboratory Assessments

Subjects who experience disease progression (PSA or radiographic) before the end of 24 months should complete laboratory assessments at the Progression Visit as outlined in the Study Schedule. During the Off-therapy Follow up Period laboratory assessments include the following:

- Serum PSA level at the end of every 2 months (see Section 10.6).
- Peripheral blood collection for measurement of serum testosterone levels at the end of every 2 months (see Appendix **6** for collection, processing, and shipping instructions).
- Fasting glucose, fasting lipid panel (total cholesterol, LDL, HDL, triglyceride), and hemoglobin A1C at the end of Months 18 and 24.
- Peripheral blood collection for measurement of fasting serum insulin at the end of Months 18 and 24 (see Appendix **6**).

### 7.6.4 Radiographic Assessment

A whole body nuclear bone scan, along with cross-sectional imaging of the abdomen/pelvis (CT or MRI; with IV contrast per individual investigator discretion), will be obtained as prompted by signs and symptoms of metastatic disease and at the time of PSA progression.

Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast or without, as long as method is identical each time new scans are done

There will be no central reading of the scans and radiographic progression will be based upon investigator assessment.

## 7.7 FOLLOW UP PERIOD (MONTH 25+)

Subjects without progressive disease (PSA or radiographic) at end of 24 months will enter a Follow-up Period. During this period, subjects will be followed by history and physical exam, serum PSA, and testosterone levels every 3 months. Subjects who develop PSA or radiographic

progression, or initiate non-protocol therapy will be removed from study and treated as per individual investigator discretion.

If no progressive disease occurred during Months 1 to 24 and it occurs during the Follow-up Period, whole blood RNA and plasma sample collections for biomarker testing should be collected from subjects who consented to this optional sample collection (see Section 7.2, Appendix 6).

### 7.8 REASONS FOR STUDY DISCONTINUATION

Subjects will discontinue study protocol treatment for the following reasons, whichever comes soonest:

- PSA progression, defined as an increase in PSA to > 50% of the baseline value or an increase of > 2 ng/mL above the nadir, whichever is higher, confirmed by repeat measurement at least 2 weeks later.
- Radiographic progression, defined as the detection of new metastasis on either bone scan or cross-sectional imaging (CT or MRI).
- Subject or treating physician decision
- Unacceptable toxicity
- Non-protocol therapy

Efforts will be made to ensure that subjects who discontinue in the absence of progressive disease (PSA or radiographic) enter the Off-therapy Observation Period or the Follow-up Period (see also Sections 7.5, 7.6 and 7.7).

# 8 STUDY DRUG INFORMATION

## 8.1 ARN-509

**Drug Substance:** ARN-509 drug substance is an almost white to slightly brown powder

**Chemical Name:** (4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-*N*-methylbenzamide)

**Molecular Formula:** $C_{21}H_{15}F_4N_5O_2S$

**Molecular Weight:** 477.44

**Formulation:** The ARN-509 tablet supplied for this study contains 60 mg of JNJ-56021927. It will be manufactured and provided under the responsibility of the Sponsor. Refer to the Investigator's Brochure for a list of excipients.

**Packaging, Storage, and Labeling:** The ARN-509 60-mg tablets will packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant caps. Study drug labels will contain information to meet the applicable regulatory requirements

**Dose and Administration**

ARN-509 will be administered orally on a continuous daily dosing regimen at a dose of 240 mg per day (4 x 60-mg tablets) with or without food.

The switch to tablets for subjects who are receiving softgel capsules will occur at the start of the next cycle (onsite visit). Each softgel capsule contains 30 mg of active drug, and each tablet contains 60 mg of active drug. The conversion from the softgel capsules to the tablet formulation **is 2:1** (Table 1).

**Table 1 Softgel Capsule to Tablet Conversion**

| Dose | Number of Softgel Capsules | Number of Tablets |
|---|---|---|
| 240 mg | 8 | 4 |
| 180 mg | 6 | 3 |
| 120 mg | 4 | 2 |

**Drug Supply:** Study drug will be provided free of charge to subjects enrolled on this study by the company Sponsor. ARN-509 is to be ordered directly from a designee indicated by the study Sponsor.

**Dispensing of Drug:** Sufficient study drug for the next cycle of therapy will be provided to subjects randomized to one of the two ARN-509 treatment arms at each monthly study visit.

**Inventory and Control:** The ARN-509 used for this study must be maintained under adequate security and stored in the pharmacy at the study site until dispensing or their destruction at each study site's investigational pharmacy. Investigators may not supply study medication to any person not enrolled in this study or to any person not named as a sub-investigator. In addition,

the investigator must maintain an accurate, running inventory of all drug supplies received and dispensed during conduct of the study.

**Return of Clinical Supplies:** Upon completion or termination of the study, all used and unused original study drug bottles, whether empty or containing study drug, should be destroyed at each study site's investigational pharmacy (or site's authorized destruction unit) following their site-specific procedure on drug destruction after the study Sponsor approves the drug destruction policy at the site. Any return shipments must provide proof of delivery, and will be accompanied by the Drug Accountability Form and a memo noting the number of bottles and quantity of study drug being returned in the site's drug accountability records. Drug will not be returned to the Sponsor.

### 8.2 LHRH AGONIST

Choice of specific LHRHa to be used in this study will be per investigator discretion/site practice guidelines. Options include Eligard®, Lupron Depot®, Zoladex®, or Trelstar®. Dosing schedule will be per individual investigator discretion.

**Route of Administration:** The LHRHa injections will be delivered either subcutaneously (Eligard®, Zoladex®) or intramuscularly (Lupron Depot® or Trelstar®) by a trained health care provider while on protocol therapy.

**Drug Supply:** The use of LHRHa in this disease setting is considered standard of care and as such will be billed to the subject's medical insurance.

**Dispensing of Drug:** Subjects will receive a LHRHa injection either subcutaneously or intramuscularly depending on the specific drug formulation.

# 9 DOSAGE MODIFICATIONS/TOXICITY

## 9.1 TOXICITY

Toxicities and Adverse Events will be assessed during each monthly clinic visit using the NCI-CTCAE Version 4.03. Because CTEP has standardized the CTCAE, the NCI does not require the inclusion of the CTCAE within this protocol document. However, all appropriate treatment areas will have access to a copy of the CTCAE Version 4.03. A copy can be downloaded from the CTEP home page: http://ctep.cancer.gov

## 9.2 DOSE MODIFICATIONS FOR ARN-509

Intrapatient dose interruptions or reductions will be permitted provided that study discontinuation criteria have not been met (Section 7.8).

- Subjects experiencing seizure of any grade or Grade 4 neurotoxicity will have protocol therapy permanently discontinued.
- For subjects experiencing Grades 1-2 treatment-related adverse events, short treatment breaks can be instituted as per the discretion of the Investigator until the severity of the toxicity decreases to Grade 1 or returns to baseline. If toxicity recurs, dose reductions to the next lower dose level will be allowed as per the discretion of the Investigator.
- For subjects experiencing Grade ≥ 3 treatment-related adverse events other than seizure, Grade 4 neurotoxicity or life threatening toxicity, study drug should be held until the severity of the toxicity decreases to Grade 1 or returns to baseline. If toxicity recurs at Grade 3 or higher, the dose of ARN-509 should be reduced to the next lower dose level. A maximum of 2 dose level reductions will be allowed (Table 2).
- Any subject requiring > 28 days delay in treatment due to AEs may meet one of the criteria for study treatment discontinuation (see Section 7.8), which must be discussed with Sponsor.

**Table 2 ARN-509 Dose Levels**

| Total Daily Dose | Number of 60-mg Tablets (QD) |
|---|---|
| 240 mg | 4 |
| 180 mg | 3 |
| 120 mg | 2 |

Doses reduced for study treatment-related toxicities should generally not be re-escalated, however, re-escalation back to the previous dose level may be permitted in consultation with the Sponsor.

## 9.3 DOSE MODIFICATIONS FOR LHRHA

There will be no mandated dose reductions or delays for LHRHa therapy due to adverse events that are typically attributed to ADT, including anemia, hot flashes, gynecomastia, fatigue, mood changes, decreased libido, erectile dysfunction, and weight gain. Unanticipated adverse events that are not included in the above list, that the investigator attributes to LHRHa therapy will be

recorded, and if Grade 3 or higher in severity for a duration of more than 4 weeks, will lead to study discontinuation due to unacceptable toxicity and treatment as per individual investigator discretion.

# 10 ASSESSMENT OF INVESTIGATIONAL PRODUCT

## 10.1 FACT-P SCALE

The FACT-P scale [version 4.0] is a well validated metric [33] developed by Cella and colleagues, which includes a 27-item "core" quality of life measure (FACT-G) grouped into 4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. There are an additional 12 items specific to prostate cancer; 10 of which are prostate cancer specific physical problems. Items are rated on a 5-item Likert scale, from 0, "not at all", to 4, "very much" (see Appendix 1). The total range of scores is from 0 – 156. Higher scores indicate higher degree of functioning and better quality of life. Internal consistency of the prostate cancer specific subscale ranged from 0.65 to 0.69, with coefficients for FACT-G subscales and aggregated scores ranging from 0.61 to 0.90. Concurrent validity was confirmed by the ability to discriminate subjects by disease stage, performance status, and baseline prostate-specific antigen (PSA) level. Sensitivity to change in performance status and PSA score over a 2-month period suggested that some subscales of the FACT-P are sensitive to meaningful clinical change [33]. Prior clinical trials have established that minimally important differences that are clinically significant and may impact treatment decisions range from 5 to 8 points depending on tumor subtype [57].

As per standard scoring guidelines for the FACT-P scale, if a subject does not answer specific items of from a subscale of the FACT-P, the weighted average of the remaining answered items will be used for scoring purposes, as long as > 50% of items are answered for that particular subscale. If there are less than 50% of items answered in a given subscale, or less than 80% of items answered overall, the FACT-P score for that particular subject will be excluded from the statistical analysis.

## 10.2 EORTC QLQ-C30/QLQ-PR25

The EORTC QLQ-C30 [version 3] is a well validated [34], and widely used measure of health-related quality of life among cancer patients. The EORTC QLQ-C30 consists of 30 items, which list the functioning and symptoms of cancer patients. Five multi-item function scales are scored: physical function (PF), role function (RF), emotional function (EF), social function (SF), and global health status/quality of life. Furthermore, nine single-item scales (symptoms) are scored, including fatigue, pain, dyspnea, and gastrointestinal problems. The scales are, according to the EORTC guidelines, linearly transformed: all scales range from 0 to 100, in which a higher scale score represents a higher level of functioning. With respect to the single-item scale, a higher score indicates more symptoms or problems; scores of these items will be inverted for the purposes of statistical analysis. In addition, a subscale related to prostate cancer (EORTC QLQ-PR25) will also be administered, consisting of 25 items, with the same linear transformation to a scale ranging from 0 to 100 (see Appendix 2).

## 10.3 SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

The Sexual Health Inventory for Men (SHIM) is a well validated [38] abridged 5-item of the 15-item International Index of Erectile Function, which has been extensively studied in men with erectile dysfunction due to various etiologies, including prostate cancer-related therapies. It consists of 5 items pertaining to sexual functioning, with scores ranging from 0-5 for most items.

Higher scores indicate higher level of sexual function and less erectile dysfunction (see Appendix 3).

## 10.4 ADMINISTRATION OF QOL QUESTIONNAIRES

The aforementioned questionnaires (FACT-P, EORTC QLQ-C30/QLQ-PC25 and SHIM) will be administered to each subject according to the study schedules (see Sections 7.1 and 7.2). The questionnaires should take approximately 20-30 minutes to complete. A designated clinical research coordinator will ensure that subjects complete the questionnaires during their study visit. If a subject stops protocol therapy due to unacceptable toxicity or progressive disease, effort will be made to ensure that subjects continue to complete QOL questionnaires according to the study schedule.

## 10.5 METABOLIC PARAMETERS

Subjects experiencing disease progression (PSA or radiographic) during either the On-therapy Period or the Off-therapy Observation Period should complete assessments required at the Progression Visit (see Study Schedules for details).

### 10.5.1 Markers of Insulin Resistance

Fasting plasma glucose, fasting serum insulin, body mass index, and hemoglobin A1C will be measured according to the study schedules (See Sections 7.1 and 7.2). Subjects must be fasting for at least 12 hours prior to collection of blood for fasting glucose and insulin measurement. If the subject is not in a fasting state at the particular time point, the fasting glucose and insulin tests will be omitted from the analysis.

Peripheral blood for fasting serum insulin level determination will be collected, shipped and banked as per instructions outlined in Appendix **6**.

### 10.5.2 Fasting Lipid Panel

The fasting lipid panel (total cholesterol, LDL, HDL, and triglycerides) will be measured at according to the study schedules (see Sections 7.1 and 7.2). Subjects must be fasting for at least 12 hours prior to collection of blood for accurate measure of fasting lipid panel. If the subject is not in a fasting state at a particular study time point, the lipid panel will not be collected on that date and omitted from these exploratory statistical analyses.

### 10.5.3 Bone Mineral Density

DEXA scans will be completed during the On-therapy Period according to the study schedule (see Section 7.1) The mean percent change in bone mineral density as measured at the femoral neck, and lumbar spine will be compared between experimental ARN-509 containing arms and control LHRHa monotherapy arm.

### 10.5.4 Serum Hormone Levels

Peripheral blood for measurement of serum hormone levels, including testosterone, estradiol, and dihydrotestosterone, will be collected, banked, and shipped as outlined in Appendix **6**. See study schedules for timing of sample collection (Sections 7.1 and 7.2).

### 10.6 PSA MEASUREMENT

Serum PSA will be measured using local CLIA-certified laboratory using an ultrasensitive assay. It is preferable that each subject has serial laboratory measurements of PSA at the same laboratory while on study.

### 10.7 OPTIONAL SAMPLE COLLECTION FOR BANKING, RNA, AND BIOMARKER ANALYSIS

Optional samples of peripheral blood will be collected for banking of plasma, serum, and PBMCs. Archival FFPE blocks or slides, whole blood for RNA testing, and biomarker collection are also optional. Please see Appendix **6** for collection, processing, and shipping instructions). Archival FFPE blocks are preferred however slides will also be accepted. Whole blood will be collected in PAXgene tubes for RNA testing for markers previously confer resistance to ARN-509 or enzalutamide. These include androgen receptor anomalies (eg: AR amplification, ARv3/7, and ARv567), AR axis genes, and other compensatory pathway markers. See Study Schedules (Section 7) for timing of optional sample collections.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and adequate sample material. Therefore, some analyses may be deferred or not done if, for any reason, the analysis will have no scientific value. Biomarker data from this study may be compared with or combined with data obtained from prior studies.

# 11 PLANNED STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used in analyzing the data is outlined in the protocol. Details will be provided in the Statistical Analysis Plan (SAP).

## 11.1 DETERMINATION OF SAMPLE SIZE AND STUDY POWER

The expected mean decline in FACT-P score and within group standard deviation for the control arm treated with 12 months of LHRHa monotherapy is 4-8 and 8-12 points, respectively, based on prior studies of measuring QOL using FACT-P among men treated with ADT [32, 58, 59]. A change in total FACT score that is clinically meaningful and impacts treatment in prior studies ranges from 5-8 points depending on cancer subtype [56]. Approximately 30 subjects will be randomized to each of the 3 treatment arms for this comparison. Accounting for a dropout/questionnaire non-completion rate of 10%, this will allow for 27 evaluable subjects per study arm. For the comparison of the mean change in FACT-P score between ARN-509 monotherapy and LHRHa monotherapy, this sample size has 80% power to detect an effect size of at least 0.86, corresponding to a difference of 7.5 points in mean 12 month change in FACT-P score between treatment groups with a common standard deviation for the change in each arm of 8.7 which is similar to the reported standard deviation for LHRHa monotherapy. This is based upon a 2 group t test, using a bidirectional level of significance of 0.025 (adjusted for 2 comparisons). To test for non-inferiority in QOL with ARN-509 + LHRHa compared with LHRHa monotherapy, inferior QOL is defined as a greater than 7 point difference in mean change in FACT-P score between the treatment groups and the common standard deviation is again assumed to be 8.7. This sample size has 82% power to reject the null hypothesis of a difference in mean score and accept the alternative hypothesis of non-inferiority with an effect size of at least 0.81, using a 2 group t-test with 2-sided $\alpha$ of 0.025.

## 11.2 CLINICAL CUTOFFS

### 11.2.1 Interim Analysis

No interim analysis will be planned for efficacy due to the expected rate of accrual, the primary endpoint being analyzed, and total sample size.

An interim safety review will be performed after 20 subjects have completed at least 1 month of therapy with either ARN-509 monotherapy or ARN-509 + LHRHa. If there are more than 5 subjects with Grade 3 or higher toxicities not related to ADT (anemia, fatigue, gynecomastia, hot flushes, decreased libido, erectile dysfunction, mood changes, and weight gain), that the study investigator deems as possibly, probably, or definitely treatment-related, the study will be terminated. This indicates that at least 30% of the subjects had unacceptable toxicities. If accrual is completed and all 60 subjects were treated with ARN-509 (with or without LHRHa) and if unacceptable toxicity is > 30%, then the exact 95% lower bound for unacceptable toxicity of 30% would be 20.4%. Study enrollment will continue during the interim safety review.

### 11.2.2 Final Clinical Cutoff

The Sponsor will establish a final clinical cutoff date after all subjects have completed the Month 24 Visit. Data collection will cease at this time. The final clinical study report will be written

based on these data. Any subjects who continue in the Follow-up Period will be discontinued from the study.

## 11.3 ANALYSIS POPULATIONS

Subject disposition, quality of life, metabolic, and PSA suppression endpoints will be assessed using data from the intent-to-treat (ITT) population. All subjects randomized into the study will be classified according to their assigned treatment group, regardless of the actual treatment received. Safety analyses will be performed using all subjects who received at least 1 dose of study drug, with treatment assignments designated according to actual study treatment.

## 11.4 METHODS FOR ANALYSIS

### 11.4.1 Analytic Plan for the Primary Endpoint

Change from baseline in FACT-P total scale will be analyzed using a mixed-model for repeated measures (MMRM). The model will include baseline scale, treatment, month (categorical), and treatment-by-month interaction as covariates. An unstructured variance-covariance matrix will be used to model within-subject errors, but simpler structures (eg, compound symmetry) may be used to ensure estimation convergence. Change from baseline will be estimated using least-squares means with factor levels weighted according to overall baseline sample means. Data up to 12 months will be included in the analysis and the primary time point of interest will be at 12 months.

Contrasts will be set up to compare ARN-509 monotherapy vs. LHRHa monotherapy and ARN-509 + LHRHa vs. LHRHa monotherapy. To test for non-inferiority with respect to ARN-509 + LHRHa compared with LHRHa monotherapy, inferior boundary is defined as a greater than 7 point difference in mean change in FACT-P total score.

The estimated least-squares mean (+/- SE) over time will be presented using a line plot.

### 11.4.2 Analytic Plan for the Secondary Endpoints

The secondary QOL endpoints will be analyzed using a similar approach as for the primary endpoint. Data up to 24 months will be included in the analysis.

<u>PSA Modulation:</u>

The proportion of subjects without PSA or radiographic progression and who have recovered serum testosterone to greater than 150 ng/dL at 24 months from Day 1 will be compared for subjects treated ARN-509 monotherapy vs. LHRHa monotherapy and for ARN-509 + LHRHa vs. LHRHa monotherapy. The proportions by treatment will be compared using the chi-square test or Fisher's exact test as appropriate. Results will be summarized at 24 months from Day 1 with 95% confidence intervals for each treatment arm. Subjects who withdraw from the study prior to 24 months after Day 1 will not be included in this analysis. Details can be found in the statistical analysis plan (SAP).

The proportion of subjects with a PSA less than 0.2 ng/mL after 7 months of protocol therapy will be analyzed using similar approaches for proportion of subjects without evidence of PSA or

radiographic progression during the 24-month treatment period and with recovery of serum testosterone at 24 months.

The probability distributions by treatment group of the time to PSA progression will be estimated using the Kaplan-Meier method. Durations will be measured from Day 1 of study treatment to the first date of PSA progression. The log-rank test will be used to compare the distribution of time to PSA progression.

Metabolic and Hormonal Parameters:

The mean change from baseline for markers of insulin resistance (including fasting glucose, insulin, body mass index, and hemoglobin A1C), fasting lipid panel (including total cholesterol, LDL, HDL, and serum triglycerides), and hormone levels (including DHT and estradiol) analyzed using a similar approach as for the primary endpoint.

The mean change in bone mineral density at the femoral neck, and lumbar spine as measured by DEXA scan will be compared for ARN-509 monotherapy vs. LHRHa monotherapy and ARN-509 + LHRHa vs. LHRHa monotherapy using an analysis of covariance (ANCOVA) that controls for baseline values of the corresponding measurement.

The time to serum testosterone recovery to > 50 ng/dL and > 150 ng/dL after the cessation of protocol therapy at 12 months will be compared for ARN-509 + LHRHa vs. LHRHa monotherapy. The probability distributions by treatment group of the time to testosterone recovery will be estimated using the Kaplan-Meier method. The log-rank test will be used to compare the distribution of time to testosterone recovery. Subjects who discontinue study drug prior to 12 months for disease progression, unacceptable toxicity, or study withdrawal, as well as subjects who continue hormonal therapy after 12 months or receive non-protocol therapy, will not be included in the analysis of this exploratory endpoint.

No adjustment for multiple comparisons will be made for the analysis of the secondary and correlative endpoints. Some correlative analyses may be deferred or not done if, for any reason, the analysis will have no scientific value.

Safety Analysis:

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Toxicities will be graded for severity according to NCI-CTCAE Version 4.03 (see Section 12.1.5). All reported adverse events with onset during the On-therapy Period up to 30 days after the last dose of study medication will be included in the analysis.

Specifically, the following adverse events will be summarized:

- All adverse events
- Grade 3 or higher adverse events
- Serious adverse events

- Adverse events leading to discontinuation of treatment
- Adverse events leading to death

Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who died, who discontinue treatment due to an adverse event, or who experience a ≥Grade 3 or higher or a serious adverse event.

In addition, abnormal findings in physical exams and laboratory tests will be summarized.

Biomarker analysis

Biomarker analyses will be conducted on archival FFPE blocks or slides, plasma and whole blood samples collected from subjects who consented to participate in biomarker analysis to assess $AR^{F876L}$ mutation and other resistance markers from all 3 treatment groups.

Further association may be made with clinical endpoints with:

- Markers identified from RNAseq analysis of archival tumor samples
- Plasma DNA at progression or end of treatment will be used to assess the frequency of $AR^{F876L}$ mutation
- Whole blood samples collected at baseline and end of treatment or progression will be used to identify the type and frequency of AR anomalies or other RNA based markers associated with ARN-509 treatment resistance or response

The association of the rest of the biomarkers with clinical response or relevant survival endpoints may be assessed using appropriate statistical methods (eg, analysis of variance [ANOVA], categorical or survival models), depending on the endpoints. Analyses may be performed within and between each treatment group. Other clinical covariates (such as baseline tumor characteristics and subject demographics) may also be included in the model. Correlation of baseline biomarker expression levels with clinical response or relevant time-to-event endpoints may be performed to identify responsive (or resistant) subgroups.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and adequate subject material. Therefore, some analyses may be deferred or not done if, for any reason, the analysis will have no scientific value. Biomarker data from this study may be compared with or combined with data obtained from prior studies.

# 12 REPORTING AND DOCUMENTATION OF ADVERSE EVENTS

## 12.1 DEFINITIONS OF ADVERSE EVENTS

### 12.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

Note: Adverse event collection starts with the signing of the ICF.

Examples of adverse events include but are not limited to:

- Abnormal test findings
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Worsening of signs and symptoms of the malignancy under study. *Disease progression assessed by measurement of malignant lesions on radiographs or other methods should* ***not*** *be reported as an adverse event.*
- Signs or symptoms resulting from dose overdose, dependency, withdrawal, abuse, and/or misuse
- Drug interactions
- Exposure in utero (pregnancy)

For laboratory abnormalities, the criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the Investigator

### 12.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) based on ICH and European Union (EU) Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death. *If the malignancy under study has a fatal outcome during the study or within the safety reporting period, the event leading to death should be reported as a Grade 5 SAE; death is an outcome and not the adverse event in itself.*
- Is life-threatening (ie, immediate risk of death from the reaction as it occurred). *It does **not** include a reaction which hypothetically might have caused death had it occurred in a more severe form.*
- Requires or prolongs inpatient hospitalization (ie, the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned)
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

Events **not** considered to be SAEs are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care or social admissions

### 12.1.3 Expectedness

An adverse event or suspected adverse reaction for ARN-509 is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. For LHRHa with a marketing authorization, the expectedness of an AE will be determined based on whether or not it is listed in the applicable package insert or summary of product characteristics.

### 12.1.4 Attribution

A suspected adverse reaction means any adverse event for which there is reasonable possibility that the study drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

The Investigator will assign attribution of the possible association of the event with the study drug using the following definitions:

**Not Related**

An adverse event that is not related to the use of the drug.

**Unlikely (doubtful)**

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

**Possible**

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

**Probable**

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

**Definitely (Very Likely)**

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

### 12.1.5 Severity

Signs or symptoms should be graded and recorded by the Investigator according to the NCI-CTCAE (Version 4.03).

Any adverse event not listed in the CTCAE will be graded as follows:

**Grade 1, Mild**: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Grade 2, Moderate**: Sufficient discomfort is present to cause interference with normal activity.

**Grade 3, Severe**: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

**Grade 4, Life-threatening**: Urgent intervention indicated.

**Grade 5, Death**: Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

## 12.2 SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

## 12.3 PROCEDURES

### 12.3.1 All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the signing of the ICF until completion of the subject's last study-related procedure (may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF, using the NCI- CTCAE V4.03. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

### 12.3.2 Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

*SAE fax:* 1-908 450-1334

Explicitly state any specific serious adverse event follow-up that is required to be recorded on the eCRF; this will ensure that a placeholder is included on the eCRF and the follow-up will occur.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

### 12.3.3 Pregnancy

Because the effect of the blinded study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant may be collected.

# 13 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

## 13.1 PROCEDURES

All initial PQCs must be reported to the Sponsor (or designee) by the study-site personnel within 24 hours after being made aware of the event. If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

# 14 DATA COLLECTION, RETENTION AND MONITORING

## 14.1 DATA COLLECTION INSTRUMENTS

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

The Clinical Research Coordinator (CRC) or designated study site personnel will complete the eCRFs within 5 days following a subject visit and queries are to be addressed within 5 days from the date issued. The Investigator will review and approve the completed eCRFs. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

If corrections to an eCRF are needed after removal of the original eCRF copy from the investigational site, a data correction form (DCF) will be used.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager can generate a query for resolution by the investigational staff
- Clinical data manager can generate a query for resolution by the investigational staff

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. The information collected on eCRFs shall be identical to that appearing in original source documents. Source documents will be found in the subject’s medical records maintained by study site personnel. All source documentation should be kept in separate research folders for each subject.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs. Each eCRF must be reviewed for accuracy by the Investigator, corrected as necessary, and then approved. Alternatively, the Investigator may sign individual, printed eCRFs. These signatures attest that the information contained on the eCRFs is true and accurate. A copy of the eCRF will remain at the Investigator's site at the completion of the study.

At study completion, when the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement among Aragon Pharmaceuticals, the Study Chair, the Trial Statistician, and the Protocol Project Manager at UCSF.

### 14.2 DATA QUALITY CONTROL AND REPORTING

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources. Queries are entered, tracked, and resolved through the eDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

### 14.3 ARCHIVAL OF DATA

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim and final reports), data for analysis is locked and cleaned per established procedures.

### 14.4 AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer, but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of ARN-509.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another

investigator, another institution, or to the Sponsor itself. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

### 14.5 MONITORING

Monitoring visits will be conducted by representatives of the Sponsor according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

### 14.6 SUBJECT CONFIDENTIALITY

In order to maintain subject confidentiality, only a site number and subject number will identify all study subjects on eCRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Trial Agreement.

# 15 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according in accordance with the US FDA regulations, the International Conference on Harmonisation (ICH) E6 Guidelines for GCP, and applicable local, state, and federal laws.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

## 15.1 PROTOCOL AMENDMENTS

Any amendment to the protocol will be written in collaboration by UCSF with the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IECs are notified within five working days.

## 15.2 INSTITUTIONAL REVIEW BOARDS AND INDEPENDENT ETHICS COMMITTEES

The protocol, Investigator's Brochure, the consent forms, any information to be given to the subject (including subject recruitment materials) and relevant supporting information must be submitted to the IRB/IEC by the Investigator for review and approval before the study is initiated. Any member of the IRB/IEC who is directly affiliated with this study as an Investigator or as site personnel must abstain from the IRB/IEC vote on the approval of the protocol. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor (or designee) prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

Investigators are required to promptly report to their respective IRB/IEC all unanticipated problems involving risk to human subjects. Some IRBs/IECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory

requirements and with the policies and procedures established by their IRB/IEC and archived in the site's study file.

Finally, the Investigator will keep the IRB/IEC informed as to the progress of the study, revisions to documents originally submitted for review, annual updates and/or request for re-approvals, and when the study has been completed.

### 15.3 INFORMED CONSENT FORM

Informed consent will be obtained in accordance with the ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a, b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Sponsor's master ICF will be provided to each site. Sponsor or its designee must review and approve any proposed deviations from the master ICF or any alternate consent forms proposed by the site before IRB/IEC submission. Subjects must be re-consented to the most current version of the consent forms during their participation in the study. The final IRB/IEC-approved consent forms must be provided to Sponsor for regulatory purposes.

The consent forms must be signed by the subject or the subject's legal representative before his participation in the study. The case history for each subject shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed consent form must be provided to the subject or the subject's legal representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the subject to participate.

For any updated or revised consent forms, the case history for each subject shall document the informed consent process and that written informed consent was obtained for the updated/revised consent form for continued participation in the study. The final revised IRB/IEC-approved ICF must be provided to Sponsor for regulatory purposes.

### 15.4 REPORTING OF SAFETY ISSUES AND SERIOUS BREACHES OF THE PROTOCOL OR ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the World, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

### 15.5 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of ARN-509 at any time.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the Investigator must notify the respective IRB/IEC, and contact all participating subjects and the hospital pharmacy (if applicable) within a 4-week time period. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

### 15.6 USE OF INFORMATION AND PUBLICATION

All information, including but not limited to information regarding ARN-509 or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of ARN-509, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain eCRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's database]. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarkerr analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in

writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

**Registration of Clinical Studies and Disclosure of Results**

The Sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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## Appendix 1. FACT-P

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | **PHYSICAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | **SOCIAL/FAMILY WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| P1 | I have aches and pains that bother me | 0 | 1 | 2 | 3 | 4 |
| P2 | I have certain parts of my body where I experience pain | 0 | 1 | 2 | 3 | 4 |
| P3 | My pain keeps me from doing things I want to do | 0 | 1 | 2 | 3 | 4 |
| P4 | I am satisfied with my present comfort level | 0 | 1 | 2 | | 4 |
| P5 | I am able to feel like a man | 0 | 1 | 2 | 3 | 4 |
| P6 | I have trouble moving my bowels | 0 | 1 | 2 | 3 | 4 |
| P7 | I have difficulty urinating | 0 | 1 | 2 | 3 | 4 |
| BL2 | I urinate more frequently than usual | 0 | 1 | 2 | 3 | 4 |
| P8 | My problems with urinating limit my activities | 0 | 1 | 2 | 3 | 4 |
| BL5 | I am able to have and maintain an erection | 0 | 1 | 2 | 3 | 4 |

# Appendix 2. EORTC QLQ-C30/QLQ-PR25

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

## EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the past week | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|
| 31. Have you had to urinate frequently **during the day**? | 1 | 2 | 3 | 4 |
| 32. Have you had to urinate frequently **at night**? | 1 | 2 | 3 | 4 |
| 33. When you felt the urge to pass urine, did you have to hurry to get to the toilet? | 1 | 2 | 3 | 4 |
| 34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate? | 1 | 2 | 3 | 4 |
| 35. Have you had difficulty going out of the house because you needed to be close to a toilet? | 1 | 2 | 3 | 4 |
| 36. Have you had any unintentional release (leakage) of urine? | 1 | 2 | 3 | 4 |
| 37. Did you have pain when you urinated? | 1 | 2 | 3 | 4 |
| 38. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you? | 1 | 2 | 3 | 4 |
| 39. Have your daily activities been limited by your urinary problems? | 1 | 2 | 3 | 4 |
| 40. Have your daily activities been limited by your bowel problems? | 1 | 2 | 3 | 4 |
| 41. Have you had any unintentional release (leakage) of stools? | 1 | 2 | 3 | 4 |
| 42. Have you had blood in your stools? | 1 | 2 | 3 | 4 |
| 43. Did you have a bloated feeling in your abdomen? | 1 | 2 | 3 | 4 |
| 44. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 45. Have you had sore or enlarged nipples or breasts? | 1 | 2 | 3 | 4 |
| 46. Have you had swelling in your legs or ankles? | 1 | 2 | 3 | 4 |

| During the last 4 weeks… | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|
| 47. Has weight loss been a problem for you? | 1 | 2 | 3 | 4 |
| 48. Has weight gain been a problem for you? | 1 | 2 | 3 | 4 |
| 49. Have you felt less masculine as a result of your illness or treatment? | 1 | 2 | 3 | 4 |
| 50. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 51. To what extent were you sexually active (with or without intercourse)? | 1 | 2 | 3 | 4 |

**PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS**

| | | | | |
|---|---|---|---|---|
| 52. To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |
| 53. Did you have difficulty getting or maintaining an erection? | 1 | 2 | 3 | 4 |
| 54. Did you have ejaculation problems (eg dry ejaculation)? | 1 | 2 | 3 | 4 |
| 55. Have you felt uncomfortable about being sexually intimate? | 1 | 2 | 3 | 4 |

# Appendix 3. Sexual Health Inventory for Men (SHIM)

## SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

**PATIENT NAME:** _____ **TODAY'S DATE:** _____

**PATIENT INSTRUCTIONS**

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question**.

**OVER THE PAST 6 MONTHS:**

| | | | | | | |
|---|---|---|---|---|---|---|
| **1.** How do you rate your confidence that you could get and keep an erection? | | VERY LOW | LOW | MODERATE | HIGH | VERY HIGH |
| | | 1 | 2 | 3 | 4 | 5 |
| **2.** When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)? | NO SEXUAL ACTIVITY | ALMOST NEVER OR NEVER | A FEW TIMES (MUCH LESS THAN HALF THE TIME) | SOMETIMES (ABOUT HALF THE TIME) | MOST TIMES (MUCH MORE THAN, HALF THE TIME) | ALMOST ALWAYS OR ALWAYS |
| | 0 | 1 | 2 | 3 | 4 | 5 |
| **3.** During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? | DID NOT ATTEMPT INTERCOURSE | ALMOST NEVER OR NEVER | A FEW TIMES (MUCH LESS THAN HALF THE TIME) | SOMETIMES (ABOUT HALF THE TIME) | MOST TIMES (MUCH MORE THAN, HALF THE TIME) | ALMOST ALWAYS OR ALWAYS |
| | 0 | 1 | 2 | 3 | 4 | 5 |
| **4.** During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? | DID NOT ATTEMPT INTERCOURSE | EXTREMELY DIFFICULT | VERY DIFFICULT | DIFFICULT | SLIGHTLY DIFFICULT | NOT DIFFICULT |
| | 0 | 1 | 2 | 3 | 4 | 5 |
| **5.** When you attempted sexual intercourse, how often was it satisfactory for you? | DID NOT ATTEMPT INTERCOURSE | ALMOST NEVER OR NEVER | A FEW TIMES (MUCH LESS THAN HALF THE TIME) | SOMETIMES (ABOUT HALF THE TIME) | MOST TIMES (MUCH MORE THAN, HALF THE TIME) | ALMOST ALWAYS OR ALWAYS |
| | 0 | 1 | 2 | 3 | 4 | 5 |

**Add the numbers corresponding to questions 1-5.** **TOTAL:** _____

**The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:**

**1-7 Severe ED** **8-11 Moderate ED** **12-16 Mild to Moderate ED** **17-21 Mild ED**

# Appendix 4. ECOG Performance Status Scale

## Performance Status Score Conversion[3]

| ECOG (Zubrod)[1] | | Karnofsky[2] | |
|---|---|---|---|
| Score | Description | Score | Description |
| 0 | Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light housework, office work. | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or do normal work. |
| 2 | Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated.<br>Death not imminent. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated.<br>Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |

1. Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: *Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol* 5:649-655, 1982.

2. Karnofsky, D. A., Abelmann, W. H., Craver, L. F., and Burchenal:.*The use of nitrogen mustards in the palliative treatment of cancer. Cancer* 1:634-656, 1948.

3. National Cancer Institute – Cancer Therapy Evaluation Program: *Clinical Data Update System (CDUS), Instructions and Guidelines.* Version 3.0 release 5, 11 January, 2011.

## Appendix 5. List of Medications and Supplements Either Prohibited Or Not Recommended While On Study:

### Medications/Supplements Which Are **PROHIBITED** While On Study:

Aldactone
Aminophylline
Amitriptyline
Bicalutamide
Buproprion
Chemotherapy
Chlorpromazine
Clozapine
Cyproterone acetate
Diethylstilbesterol
Degarelix
Desipramine
Doxipine
Dutasteride
Estrogens
Finasteride
Fluconazole
Flutamide
Imipramine
Immunotherapy
Itraconazole
Ketoconazole
Lithium
Maprotiline
Megestrol
Meperidine
Mesoridazine
Milk thistle
Mirtazapine
Nilutamide
Olanzapine
Other investigational agents
PC-SPES
Pethidine
Pomegranate extract
Pomegranate juice
Progesterones
Radiotherapy other than prevention/treatment of painful gynecomastia
Saw palmetto
Spironolactone

Steroids at an equivalent dose of prednisone 5 mg per day or higher
Theophylline
Thioridazine
Ziprasidone

## Medications/Supplements Which Are **RESTRICTED** While on Study (Monitor for Increased Toxicity/Potential Drug Interactions):

**Drug Interactions:** In vitro, CYP3A4 and CYP2C8 are the enzymes primarily responsible for the metabolism of ARN-509. Co-administration of a strong CYP3A4 inhibitor (itraconazole) had no clinically meaningful effect on the PK of ARN-509 and its active metabolite ARN00308. Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the AUC of ARN-509 by 68% but decreased the AUC of ARN00308 by 15%. The effects of CYP3A4 inducers or CYP2C8 inducers on the PK of ARN-509 have not been evaluated in vivo. Co-administration of ARN-509 with the following drugs that can induce CYP3A4 or CYP2C8 should be avoided as co-administration with any of these agents may decrease ARN-509 plasma concentrations. Alternative therapies should be used when available.

- Strong CYP3A4 inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort
- CYP2C8 inducers: rifampin

# Appendix 6. Peripheral Blood Collection, Processing, and Shipping Instructions

Peripheral blood for measurement of serum testosterone, dihydrotestosterone, estradiol, and fasting insulin levels will be collected at each site according to the instructions outlined below, and shipped to a central laboratory for analysis. Specimens should be shipped within 1 month of date of collection.

Peripheral blood and urine collection for banking of peripheral blood mononuclear cells (PBMC), plasma, serum, and urine is optional. Specimens will be banked at a central laboratory.

## I. Subject Confidentiality

Prior to the date of collection of each sample to be shipped to a central laboratory, the local CRC should notify the lead center CRC that specimen is to be collected at the subject's next visit. The lead center CRC will then assign unique specimen log numbers to be written on the specimen vials; this will ensure subject confidentiality.

A central laboratory will serve as a repository for banking human samples. The samples will receive a subject-insensitive identifier and the link to subject identity will be kept in a locked file with access only by the director of the Tissue Bank. Other investigators will have access to the samples only through established Tissue Core procedures. That is, investigators must submit a written request to use the stored samples as part of a CHR-approved protocol that is reviewed by the Tissue Core committee. This review limits the testing that can be done on these samples. Subjects have the right at any time to request that all remaining samples be destroyed. The subject or relatives may be contacted about future, additional research on stored samples, if necessary. Additional written consent will be required if additional samples are to be taken.

## II. Serum Hormone Measurements

At baseline, after month 3, 6, 9, and 12, **fifteen** mL of whole blood will be collected in two red top tubes (no gel) and centrifuged at 3000 rpm for 10 minutes. The serum will be decanted into three 2mL polypropylene screw cap (leak-proof) vials that have been properly labeled with the unique specimen log numbers provided and stored at -80°C until shipment to a central laboratory.

After month 14, 16, 18, 20, 22, and 24, **five** mL of whole blood will be collected in one red top tube (no gel) and centrifuged at 3000 rpm for 10 minutes. The serum will be decanted into one 2 mL polypropylene screw cap (leak-proof) vial with the proper label and stored at -80°C until shipment to a central laboratory.

Serum testosterone, estradiol, and dihydrotestosterone levels will be measured in batched samples using liquid chromatography/tandem mass spectrometry (LC/MS/MS).

## III. Fasting Plasma Insulin Measurement

At baseline, after month 3, 6, 9, 12, 18, and 24, **five** mL of whole blood will be collected in one red top tube (no gel) and centrifuged at 3000 rpm for 10 minutes. The serum will be decanted into one 2 mL polypropylene screw cap (leak-proof) vial that has been properly labeled with the unique specimen log numbers provided at stored at -80°C until shipment to a central laboratory.

## IV. Banking of Peripheral Blood, Plasma, and Serum (Optional)

At baseline, after month 3, 6, 9, and 12, **twenty** mL of whole blood will be collected in one tigertop tube (serum) and one lavender top tube (plasma) and centrifuged at 3000 rpm for 10 minutes. The serum and plasma will be decanted into two 2mL polypropylene screw cap (leak-proof) vials (four total vials) that have been properly labeled with the unique specimen log numbers provided and stored at –80°C until shipment to a central laboratory.

At baseline, after month 3, 6, 9, and 12, urine should be collected and decanted into two 2mL polypropylene screw cap (leak-proof) vials labeled with the assigned specimen log numbers and stored in refrigerator until shipment to a central laboratory.

At baseline, **twelve** mL of whole blood in 2 plastic EDTA tubes will also collected and freshly frozen at -80°C until shipment to a central laboratory.

## V. Archival FFPE Blocks or Slides, Plasma and Whole Blood for Biomarker Testing (Optional)

Archival FFPE blocks or slides will be collected from consented subjects any time after enrolling into the study. Ship Archival FFPE blocks or slides ambient to a central laboratory. Whole blood samples will be collected at baseline end of treatment and progression. Blood (2.5ml) will be collected in PAXgene™ Blood RNA tube. PAXgene tube should be at room temperature (18-25°C) prior to use. To prevent backflow, place donor's arm in a downward position. Hold tube in a vertical position, below the donor's arm during blood collection. Release tourniquet as soon as blood starts to flow into tube. Make sure tube additives do not touch stopper or end of the needle during venipuncture. Ensure that blood has stopped flowing into the PAXgene tube before removing the tube from the holder (at least 10 seconds). Gently invert the PAXgene tube 8-10 times. Always leave the PAXgene tube as the FINAL TUBE to draw. If the PAXgene tube is the only tube required, collect blood into a 2 mL discard tube prior to collecting the PAXgene tube. The discard tube must be filled with at least 2 mL of blood to flush the air from the tubing.

Be sure to follow complete PAXgene collection and sample handling instructions, which are provided with the tubes. Label tube with unique specimen identification numbers, which will be provided. Store samples at –80°C until shipped to a central laboratory.

Peripheral blood (10 ml) will be collected in K2EDTA tubes at end of treatment and progression. Centrifuge at room temperature for 10 minutes at 1600 (±150) g. After centrifugation, transfer supernatant of the EDTA tube (using a disposable pipette) to one fresh 15 ml labeled centrifuge tube. Centrifuge the plasma in the 15 ml centrifuge tube at room temperature for 10 min at 3000 (±150) g. After centrifugation, transfer supernatant to a fresh 15 ml centrifuge tube without disturbing the cellular layer using a disposable pipette. Be sure to pre-label this transfer tube. After transferring the plasma to a new 15 ml centrifuge tube as described, gently mix plasma.

Transfer 1ml plasma each into (2) 2ml labeled cryovials provided.

Place cryo tubes into a storage box and freeze upright. Store samples at -80°C until shipped to a central laboratory. Ship both aliquots (primary and back-up) together in your shipment.

## VI. Shipping Instructions

Specimens may be batch-shipped on dry ice by overnight delivery Mondays-Thursdays. For specimens to be shipped to a central laboratory, the local coordinator should notify the lead center coordinator at the central laboratory prior to specimen shipment. As for the specimens to be shipped to a central laboratory (archival FFPE blocks or slides, plasma and whole blood for biomarker testing [optional samples]), please refer to the Central Laboratory Manual for the shipping instructions.