Official Title	TRAMP: Tumor Necrosis Factor- α Blockade and AR Inhibition in Men with CRPC
NCT Number	NCT05960578
Document Type	Study Protocol and Statistical Analysis Plan
Document Date	5/20/2026

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7.6 Dosing Delays/Dose Modifications

Refer above to sections 7.3.1.1. (Golimumab Dose Modifications) and 7.3.2.1 (Apalutamide Dose Modifications).

8.0 SUBJECT EVALUATION

8.1 Clinical Evaluations

Clinical evaluations take place according to the Study Calendar (Appendix A). The sections below detail the types of evaluations to be performed during this study, as well as the timing of the assessments.

8.2 Screening and Baseline Evaluations

The screening period is 42 days before the first dose of golimumab. Subjects must meet all of the inclusion and none of the exclusion criteria. All information required for determining eligibility must be available prior to C1D1. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening phase.

Procedures to be performed during the Screening/Baseline Visit are as follows:

- Informed consent obtained
- Comprehensive Physical Examination including vital signs
- Performance Status (ECOG)
- Labs:
    - PSA (prostate specific antigen)
    - Serum Testosterone
    - Hematology: CBC, differential, platelets
    - Comprehensive Metabolic Panel (CMP)
    - PT/INR and PTT
    - QuantiFERON Gold (latent TB)
    - HIV
    - Hepatitis panel (Hepatitis C antibody (HCV Ab) reflex to HCV RNA PCR if HCV Ab positive. Hepatitis B battery (including surface antigen (HBsAg) with reflex to HBV DNA PCR, hepatitis B core antibody (HBcAb), anti hepatitis B surface antibody).
    - Research specific lab collection (baseline cytokines, cfDNA, PBMC)
- Radiographic assessments: CT chest/abdomen/pelvis, NM bone scan, PSMA PET scan
- Electrocardiogram (EKG)
- Metastatic tumor biopsy
- Research specific lab collection (baseline cytokines, cfDNA, PBMC)

8.3 Treatment Cycle Evaluations

For institutional standard of care regimens (e.g., LHRH agonists/antagonists and apalutamide), please refer to the existing treatment plans in Epic.

The following evaluations will be performed prior to administration of golimumab on the day of dosing.

- Physical Examination
- Vitals (within 30 minutes prior to dosing golimumab)
- Performance Status (ECOG)
- Labs:
    - PSA (prostate specific antigen)
    - Hematology: CBC, differential, platelets
    - Comprehensive Metabolic Panel (CMP)

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- Research specific lab collection (baseline cytokines, cfDNA, PBMC)

The following evaluations will be performed following administration of the investigational product.

- Vital Signs (10 minutes after golimumab administration. Note: C1D1 patients will be monitored for 2 hours and beginning C2D1 patients will be monitored for 30 minutes post-golimumab administration, etc.)
- AE Assessment
- Concomitant Medications

The following radiographic evaluations will be performed every 8-12 weeks per study calendar.

- Radiographic assessments: CT chest/abdomen/pelvis, NM bone scan
  (Note: PSMA PET scan will be recommended in screening as SOC, 12 weeks ($\pm$ 7 days) after initiation of golimumab, and at time of disease progression as SOC.)

8.4 End of Study and End of Treatment (EOT) Visit Schedule and Procedures

Subjects may discontinue treatment for any reason (see section 10.0, Subject Discontinuation of Active Treatment), however all subjects will come off-study if they experience clinical or radiographic progression while on combination apalutamide and golimumab or apalutamide monotherapy. Serologic progression alone is allowed and is not grounds for discontinuation of study, unless treating physician and patient opt to discontinue study. EOT Visits for all subjects who discontinue from the study should occur at least 7 days, but ≤ 30 days, after the last dose of golimumab and/or prior to beginning other treatment. Procedures to be performed during the EOT Visit include:

- Physical Examination
- Vitals
- Performance Status (ECOG)
- Labs:
  - PSA (prostate specific antigen)
  - Hematology: CBC, differential, platelets
  - Comprehensive Metabolic Panel (CMP)
  - Research specific lab collection (baseline cytokines, cfDNA, PBMC)
- Radiographic assessments: CT chest/abdomen/pelvis, NM bone scan, PSMA PET scan
- AE Assessment
- Concomitant Medication

8.5 Post-Treatment Follow-up Period

Subjects will have visits every 90 days after EOT as per SOC for management and treatment of castration-resistant prostate cancer for up to one year. Assessments to be performed at these visits are as per the existing treatment plans in Epic.

Once these visits and assessments have been completed, the subject will be considered as having completed participation in the clinical trial. If a subject enrolls in another study or requires additional cancer treatment, the visits may be performed earlier than the timepoints specified. If a subject is unable/unwilling to return for any scheduled visits after the EOT, the subject will be considered as having completed study requirements at the EOT.

8.6 Long-Term Follow-up Period

Subjects will be contacted by site staff by telephone, email, or mail at 6 and 12 months after the EOT visit to gather information about disease progression and survival.

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8.7 Immunological Studies

Please also refer to section 2.1.3 (Planned Exploratory Objectives). Correlative work will be exploratory in nature and will seek to determine biomarkers predictive of response to combination therapy and deconvolute changes in the tumor microenvironment as well as changes in the AR-activity scores. Examples of correlative work may include: 1) identification of proinflammatory cytokine signatures that are associated with response and resistance to treatment using peripheral and intra-tumoral cytokine concentrations, 2) characterization of the change in AR-activity scores within tumor cells and lymphocytes comparing pre-treatment Digital Spatial Profiling (DSP) assessments to those determined while on-treatment, 3) IHC protein expression validation of immune cell surface markers and lymphocyte subtypes.

Samples will be stored in appropriate media and temperature the Nelson lab (please refer to lab manual) until enough acquired for batch analysis.

9.0 TOXICITY MONITORING

Both acute and chronic toxicities are recorded. Monitoring for acute toxicity takes place during and immediately following IP administration for a period of 2 hours at the study site. Subjects are observed for the development of an immediate localized allergic reaction or anaphylactic reaction during this time.

Acceptable toxicity treatments will include Tylenol, Benadryl, IV steroids, IVF, and epinephrine if needed.

Severity of adverse events and toxicity will be recorded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

10.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

Subjects may be removed from this study at any time at their discretion. Subjects may also be removed from this protocol if they develop any untoward side effects from the study medications. In addition, there are stopping rules in place for lack of efficacy and excessive toxicity as detailed in the statistical section. Patients who do not have PSA decline at 12 weeks, should discontinue and change to alternative lines of therapy at the discretion of their treating physician.

If a subject withdraws consent to participate in the study or aspects of the study, attempts should be made to obtain permission to record survival data up to the protocol-described end of the subject follow-up period. Survival data are important to the integrity of the final study analysis. Documentation in the medical record should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

If a subject is transferred to hospice care, the subject will be considered withdrawn from the study. Attempts may be made to obtain permission to record survival data up to the protocol-described end of the subject follow-up period. Documentation in the medical record should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

Up to three subjects may be replaced if withdrawn from investigational trial treatment. More than this may be considered in conversation with the sponsor.

An explanation for discontinuing treatment is recorded for each subject discontinuing treatment on the appropriate CRF/eCRF. The Sponsor, or its designee, must be notified immediately if a subject discontinues treatment. All subjects, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- if the Sponsor decides to stop the study;
- at Investigator's discretion;
- at the subject's request;

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- if the subject enrolls in a trial of another investigational agent;
- Grade 4 or life-threatening toxicity (See Section 12, Adverse Events) attributable to study agent;
- development of second malignancy

11.0 CONCOMITANT MEDICATIONS

Medications taken at the start of the study will be documented/recorded in source and in CRFs.

- Subjects may use topical or inhaled corticosteroids, as well as corticosteroids used as replacement therapy for adrenal steroids, e.g., <0.75 mg of dexamethasone, or equivalent.
- Subjects may take doses of nonprescription strength NSAIDS, acetaminophen (paracetamol), ibuprofen or acetylsalicylic acid (aspirin) for non-chronic headache, muscle pain, trauma, or prophylaxis as long the dosing regimens comply with the recommended dose in the product labeling.
- Subjects may take vitamin supplements within a dose range not associated with toxicity.
- Other treatments and medications that may affect immune function, that have known or suspected anti-tumor activity, or that could interfere with the imaging assessment of disease progression are not allowed for subjects.
- The use of other investigational agents is not permitted.
- Active immunotherapy is not allowed for any subject.

Prohibited Concomitant Medications

As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [$GABA_A$] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below:

- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperedine and pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine

Restricted Concomitant Medications

Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 should be avoided as much as possible. Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index. Examples of the strong CYP3A4 inhibitors and inducers include the following:

- Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits); co-administration with any of these agents may increase apalutamide plasma concentrations
- Strong CYP inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort; co-administration with any of these agents may decrease apalutamide plasma concentrations

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The potential for drug-drug interaction between apalutamide and warfarin (e.g., Coumadin) is unknown at present. If a subject is taking warfarin, re-assess PT (prothrombin time)/international normalized ratio (INR) as clinically indicated and adjust the dose of warfarin accordingly.

12.0 ADVERSE EVENTS

12.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product; the event does not necessarily have a causal relationship with study drug administration or usage. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding deemed clinically significant), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

12.2 Serious Adverse Event

An AE is classified as a serious adverse event (SAE) if it meets one of the following criteria:

Fatal	The AE resulted in death.
Life threatening	The AE placed the subject at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization	The AE required or prolonged inpatient hospitalization. See Section 12.2.1 for additional details.
Disabling/incapacitating	The AE resulted in a persistent or significant disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth defect	An adverse outcome in a child or fetus of a subject exposed to the molecule or treatment plan regimen before conception or during pregnancy.
Medically significant	Any untoward medical occurrence that is considered medically significant. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, based on appropriate medical judgement, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the list 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 hospitalization, or development of drug dependency or drug abuse or malignancy.
Suspected transmission of any infectious agent via administration of a Janssen Product(s) under study.	

12.2.1 Hospitalization Reporting

For reports of hospitalization, it is the sign, symptom or diagnosis which led to hospitalization that is the serious event for which details must be provided. Any event requiring hospitalization or prolongation of

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hospitalization that occurs during 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 (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into a study. [Note: Hospitalizations that were planned before the signing of 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.]
- Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups.
- Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.

12.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

12.4 Adverse Event of Special interest

Adverse events of special interest are events that the Company is actively monitoring as a result of a previously identified signal (even if non-serious). Adverse events of special interest of **Golimumab** will be reported to the Company as defined in the protocol. In case of any amendments to the AESI list, Company will notify the Collaborative Study Partner (Sponsor-Investigator) and the Collaborative Study Partner (Sponsor-Investigator) will inform sites. Collaborative Study Partner (Sponsor-Investigator) will ensure that these changes are updated in the protocol as soon as practical.

There are no adverse events of special interest identified for **Apalutamide.**

<u>The adverse events of special interest identified for **Golimumab** are:</u>

- Serious infections
- Demyelinating disorders
- Malignancy (except prostate cancer)
- Serious depression including suicidality.
- New colon cancer/dysplasia in patients with ulcerative colitis
- Exposure during pregnancy

12.5 Monitoring and Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug, a study procedure, or other causality

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- The action taken due to the adverse event
- The outcome of the adverse event

Subjects that terminate the trial early or experience a non-serious AE considered to be possibly or definitely related to study treatment will receive EOT visit 30 days after termination of trial with appropriate long-term follow-up phone calls (as per section 8.6) if standard of care not continued at the site of trial (Fred Hutch).

12.6 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

12.7 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

Definite (must have all 4)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the participant's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure
Probable (must have 3)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the participant's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with reduction in dose or cessation of intervention
Possible (must have 2)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the participant's clinical state • Could not readily have been due to environmental or other interventions • Follows a known pattern of response to intervention
Unlikely (must have 2)	• Does not have a temporal relationship to the intervention • Could readily have been produced by the participant's clinical state • Could have been due to environmental or other interventions • Does not follow a known pattern of response to intervention • Does not reappear or worsen with reintroduction of intervention

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

12.8 Adverse Event Recording Period

AEs will be monitored and recorded in study-specific case report forms (CRFs) from time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of the product under

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study within the study. AEs with an onset date prior to the first exposure to a study intervention will not be recorded, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame. Laboratory values that are outside of normal range are not considered AEs unless they are deemed clinically significant. If deemed clinically significant, they will be monitored and recorded in study-specific CRFs.

12.9 Adverse Event Reporting Requirements

12.10 Reporting to the IRB

The investigator or designee must report events to the IRB of record in accordance with the policies of the IRB for expedited reporting and continuing review.

12.11 Reporting to FDA

The sponsor-investigator assumes responsibility for IND safety reporting to the FDA and participating investigators, in accordance with regulations under 21 CFR 312.32.

The sponsor-investigator will assess each reported event for seriousness, expectedness, and the relationship to the investigational product.

For determination of IND safety reporting, AE attribution will be assessed according to the suspected adverse reaction definition in 21 CFR 312.32, as an AE for which there is a reasonable possibility that the drug caused the adverse event, where “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reactions that are serious and unexpected will be reported to the FDA as an IND safety report.

SAEs that do not meet IND Safety Report criteria will be reported to the FDA as part of annual reporting responsibilities described under 21 CFR 312.33.]

13.0 SAFETY EVENT AND PRODUCT QUALITY COMPLAINTS REPORTING TO JANSSEN

13.1 Roles

Janssen, also referred to as the “Company”, is providing the investigational product for use in the study. For the purposes of this Study, the Janssen Products under Study are: **Apalutamide and Golimumab.**

The Sponsor-Investigator holding the IND for the study, also referred to by Janssen as the “Collaborative Study Partner”, will report safety events and product quality complaints associated with this study.

13.2 Janssen Safety Contact Information

Contact details for the Company representative for submission of information required under this section.

SAE/Pregnancy Notifications: GMS_AE_Inbo@its.jnj.comPQC: or DL-DPYIE-Globalcontacts-NIS@its.jnj.com

Phone: Contact the study assigned Janssen Trial Manager

13.3 Fax: 1-215-293-9955 Health Authority

As the Collaborative Study Partner (Sponsor-Investigator) of the Study and to the extent required by any applicable laws or regulations in each country/territory, the Collaborative Study Partner (Sponsor-Investigator) shall be responsible for complying, within the required timelines, with any safety reporting obligation towards the competent health authorities, the Ethics Committees (EC) or Independent Review Board (IRB) and the participating (co- or sub-) investigators.

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13.4 General

The Collaborative Study Partner (Sponsor-Investigator) shall notify Company immediately in case of a suspension of recruitment or premature stop of the concerned clinical study because of a safety concern; preferably by means of a telephone contact with the Company Representative, alternatively by email within twenty-four (24) hours of the decision.

Collaborative Study Partner (Sponsor-investigator) shall provide to the Company copies of any and all relevant extraordinary* (not including routine initial or follow-up ICSR submission) correspondences with health authorities and ethics committees regarding any and all serious adverse events (irrespective of the association with the Janssen Product(s) Under Study). Copies of such correspondence shall be provided within 24 hours of such report or correspondence being sent to applicable health authority.
*See definitions section 12

Training: Collaborative Study Partner (Sponsor-investigator) shall be responsible for training the Study personnel (including the Investigator) on managing safety information arising from the Study according to agreed procedures and the requirements of this Agreement.

Management of Safety Data: The Collaborative Study Partner (Sponsor-investigator) will provide safety information arising from the Study to the Company on adverse events, special situations including pregnancies and product quality complaints as defined within this exhibit (refer to section 12 Definitions). This safety information will be documented by the Investigator and reported as described in this exhibit from the first use/dose of a Janssen Product until 30 days after the last dose of the Janssen Product(s) Under Study. All subsequent AEs and SAEs beyond 30 days after the last dose of the Janssen Product(s) under study shall be collected/reported if the investigator considers the AE/SAE to be causally related to the use of the Janssen Product(s) Under Study.

Maintenance of Safety Information: All safety data arising from the Study shall be maintained in a clinical database in a retrievable format. The Collaborative Study Partner(Sponsor-investigator) shall provide a summary of all non-serious adverse events (NSAES) annually, and both serious and non-serious adverse events will be summarized in the final Study report (excluding those from subjects not exposed to a Janssen product). The summary shall include a listing of: Patient ID, adverse event term (uncoded), severity, relationship to Janssen Product(s) Under Study, and action taken with Janssen Product(s) Under Study. However, in certain circumstances more frequent provision of safety data may be necessary, e.g., to fulfill a regulatory request, and as such the safety data shall be made available within a reasonable timeframe at the Company's request.

Follow-up: All (serious and non-serious) adverse events reported for a Janssen Product(s)Under Study shall be followed up in accordance with good clinical practice (GCP).

13.5 Reporting of Safety data and Product Quality Complaints (PQCs) to Company

All adverse events and special situations (including pregnancies as defined within this exhibit in Section 12 Definitions) and product quality complaint, whether serious or non-serious, related or not related, collected as per protocol design, following exposure to a Janssen Product(s) Under Study are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their evaluation concerning the relationship of the adverse event to a Janssen Product(s) Under Study.

The Collaborative Study Partner (Sponsor-investigator) will submit (and procure that the Investigator submits), to the identified Company Representative in each Country/Territory the following safety information:

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Type of report	Timelines	How to report
Serious Adverse Event, including SAE related to the device (when the Janssen Product(s) under study is a combination product)	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Adverse Events of Special Interest (AESI)	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Reports of drug exposure during pregnancy (maternal and paternal), with or without SAE.	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Reports of Suspected transmission of any infectious agent via administration of a Janssen Product, with or without an SAE	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Abnormal Pregnancy Outcomes (e.g.. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy)	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Lack of Effect (with or without a suspected adverse reaction), must be reported as an SAE.	Within 3 business days of becoming aware of the event(s).	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Product Quality Complaints, including adverse device effects and device malfunctions, (when the Janssen Product(s) under study is a combination product	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties.
Non-Serious Adverse Event* (*Not meeting other listed 3 business day reporting criteria e.g., AESI or SS)	Annually and in final study report.	Recorded in CRF and reported annually and in final study report.
Follow-up information	Transmitted within the same timeframes as above i.e., if initial report was required to be submitted within 3 business days, follow-up information shall be submitted within the same timeframe.	Transmitted via same method as above i.e., if initial method of transmission was on an SAE form, follow-up information shall be transmitted in the same manner.

The Collaborative Study Partner (Sponsor-Investigator) responsible for ensuring that these cases are complete and if not, are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received.

Note: In the event the Study is blinded, for any events considered causally related, the Investigator will submit an unblinded SAE or pregnancy exposure report to Company.

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If the Investigator/agent of the Investigator receives safety information and is aware it involves a non-study J&J product, it will be reported to Company, indicating it is an incidental spontaneous report discovered during the course of the study.

Pregnancy:

Because the effect of the Janssen Product(s) Under Study on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen Product(s) Under Study will be reported by the Investigator within 3 business days **of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

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

13.6 Collaborative Study Partner (Sponsor-Investigator) confirmation/review of SAEs

Company Representative or designee will provide the Collaborative Study Partner (Sponsor-Investigator) with a list of the Study's SAEs and pregnancies (previously received by the Company from the Collaborative Study Partner (Sponsor-Investigator) on a semi-annual basis. Investigator will confirm to Company that all applicable SAEs and pregnancies related to Janssen Product(s) Under Study have been reported to Company.

13.7 Company Responsibilities

Company Representative or designee will provide the Collaborative Study Partner (Sponsor-Investigator) with the following safety information:

- the most recent Local Package Insert for the determination of expectedness.
- ICF risk wording
- any new information, which becomes available during the course of the Study, which may affect the overall safety profile of the Janssen Product(s) Under Study.

14.0 ADDITIONAL REPORTING DEFINITIONS

14.1 Safety Reporting Definitions

Definitions associated with adverse event reporting are provided in Section 12.0 above.

14.2 Special Situations

The following special situations must be reported to Company with or without an associated serious adverse event (SAE):

- Drug exposure during pregnancy (paternal)
- Suspected transmission of any infectious agent via administration of a Janssen Product(s) under study.

These safety events may not meet the definition of an adverse event; however, the Parties agree that for reporting purposes, they are deemed to be adverse events.

14.3 Product Quality Complaints

A PQC may have an impact on the safety and efficacy of a Company product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the Company, and are mandated by regulatory agencies worldwide. The Company has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. The Institution agrees that Lot and/or Batch #s shall be collected, when available, for all PQC reports, including reports of failure of expected pharmacological action (i.e., lack of

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effect) of a Janssen Medicinal Product. A sample of the suspected product shall be maintained for further investigation if requested by the Company.

Any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or delivery system is considered a PQC. Not all PQCs involve a patient.

Examples of PQC include but are not limited to:

- Mislabeling or misbranding
- Information concerning microbial contamination, including a suspected transmission of any infectious agent by a product
- Any significant chemical, physical, or other changes that indicate deterioration in the distributed product
- Any foreign matter reported to be in the product
- Mixed product, e.g., two drugs are mixed-up in the packaging process
- Incorrect tablet sequence (e.g., oral contraceptive tablets)
- Insecure closure with serious medical consequences, e.g., cytotoxics, child-resistant containers, potent drugs
- Suspected counterfeit or tampered product
- Adverse Device Effects including any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation, installation, operation, or any malfunction of a medical device or combination product. This also includes any event that is a result of a use error or intentional misuse and dosing device malfunctions (e.g., auto-injector button not working, needle detaching from syringe, etc.)
- Physical defect (e.g., abnormal product odor, broken or crushed tablets, etc.)

14.4 "Extraordinary" correspondence

Correspondence with a regulatory authority or ethics committee regarding a safety issue that may impact the safety or benefit-risk balance of the Janssen Product(s) Under Study, and/or may impact patients or public health. Examples include:

- Safety issues relating to a quality defect
- Major safety issues identified with changes in the nature, severity, or frequency of known serious adverse reactions which are medically significant or the detection of new risk factors for the development of a known adverse reaction or a new serious adverse reaction.
- Major safety issues identified in the context of ongoing or newly completed post-marketing studies e.g., an unexpected increased rate of fatal or life-threatening adverse events.

15.0 CRITERIA FOR ENDPOINT EVALUATIONS

15.1 Disease Assessment Prior to Enrollment

All subjects will have serum PSA measured in the screening period. Tumor burden will be based on baseline CT scans, NM scans, and PSMA PET scans.

15.2 Definition of Progression After Enrollment

Progression after enrollment will be based on PSA progression and/or radiographic or clinical progression, whichever comes first. Tumor burden will be based on RECIST change in CT scans and PCWG3 change in NM scans (PSMA PET scans will be exploratory).

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15.3 12-week PSA50

A confirmed 12-week PSA50 response is defined as a ≥ 50% reduction in PSA from baseline to 12 weeks since IP (e.g., golimumab) initiation which requires confirmation by an additional PSA assessment at least 3 weeks later.

15.4 Time to PSA Progression

Prostate specific antigen will be calculated for all treated subjects as, after a decline from baseline, the time from the first dose of IP to the first PSA increase that is ≥ 25% and a ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (i.e., confirmed rising trend). When there is no decline from baseline, then PSA progression is a ≥ 25% increase and a ≥ 2 ng/mL increase from baseline beyond 12 weeks.

15.5 Radiographic Progression-free Survival

The duration of radiographic PFS (rPFS) will be calculated for all treated subjects with soft tissue and/or bone disease as the time from the first dose of IP to the first objective evidence of radiographic progression or death from any cause, whichever occurs first. Radiographic disease progression is defined as progressive disease by RECIST for soft tissue and PCWG3 for bone disease. The PFS will be estimated using the Kaplan-Meier method for the treated population.

15.6 Survival Time

Overall survival is defined as the time from the first dose of IP to death from any cause. Subjects who are still alive at the clinical cutoff date for the analysis will be censored at the last known alive date. The OS rate at 12 months and at 24 months will be summarized using the Kaplan-Meier method for the treated population, if available.

16.0 ASSESSMENT OF EFFICACY

16.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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Evaluable disease: Bone lesions will be considered evaluable as per PCWG3 criteria and measured using Tc-99m MDP bone scan, the standard of care for evaluating baseline disease and progression. If there is ambiguity about the appearance of the bony lesions such as traumatic
in nature or secondary to a flare reaction, then it is recommended that an alternative imaging
modality such as MRI or fine-cut CT be used to evaluate these lesions further. Recording new lesions and sites of new lesions is recommended. See below for more discussion on assessment of radiographic response and progression of bone disease (13.4.3).

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

16.2 Efficacy Parameters

14.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

14.2.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

14.2.3 Assessment of Evaluable Disease (Bone metastases):
Bone disease will be assessed for progressive disease only by PCWG3.

Progression: Will be determined as per PCWG3 recommendations using the 2+2 rule to exclude pseudo progression or flare. The 2+2 rule as per PCWG3 is defined as at least two new lesions on the first scan, with at least two additional lesions on the next (confirmatory) scan 6 weeks or more from the first scan showing progression. The date of progression is the date of the first post-treatment scan, when the first two new lesions were documented. Of note changes in intensity of uptake alone do not constitute either progression or regression. Ambiguous results can be confirmed by other imaging modalities (e.g., CT or MRI) but only positivity on the bone scan defines metastatic disease to the bone.

Disease assessments will be performed according to the Time and Events Schedule. Assessment of responses for solid tumors will be performed according to RECIST (version 1.1) by investigators. For subjects who discontinue study drug before disease progression, tumor assessments should continue as described in follow-up duration. More frequent radiological assessments are allowed, if clinically indicated/desirable. Identical methodology should be used for disease assessment at baseline, and throughout the course of the study, to characterize each identified and reported lesion to document disease status.

If symptomatic deterioration (on the basis of global deterioration of health status) occurs without documentation of radiographic progression, the clinical findings used to make this determination must be specified in the eCRF and documented in the source documents. Every effort should be made to document the objective progression even after discontinuation of treatment for symptomatic deterioration. Tumor response will be reported by the investigator in the eCRF.

16.3 Method and Timing

Patients will ideally undergo CT and bone scans to assess for radiographic progression; however, MRI may substitute the CT scan with approval of the PI. PSMA PET scans will be performed once at baseline as SOC, again at time of primary endpoint 12-week after treatment (investigational), and again at EOT per SOC. PSMA PET may not be covered by patient insurance, if not covered, this is not exclusionary. Timing is outlined in the study calendar.

17.0 STATISTICAL CONSIDERATIONS

17.1 Study Design

This Phase 2, single-center, single-arm study is designed to enroll 34 patients with CRPC. This study will employ a Bayesian continual reassessment method study design with an early stopping rules for both toxicity and futility using the Bayesian method of Thall and Simon [34,35].

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Data from previous studies suggest toxicity rates leading to treatment discontinuation of below 15% for both apalutamide and golimumab. As patients are treated, if there is at least a 70% posterior probability that the true toxicity rate exceeds 30% based on the observed data, the trial will be stopped.

Similarly, it is hypothesized that efficacy rate of the combined therapy will exceed the observed response rate of 22% for apalutamide alone. The trial will be stopped early if at any point there is a 70% posterior probability that the true response does not exceed 22%.

The table below summarizes the thresholds at which the trial will be stopped for toxicity or futility.

Number of Patients Enrolled	Stop if __ or fewer responses observed	Stop if __ or more toxicities observed
5	0	2
10	1	3
15	3	5
20	4	6
25	5	7

The prior distribution selected for the toxicity rate was a beta distribution with parameters α=1.5, β=5, corresponding to a mean of 23% and a 90% credible interval 3% to 52%. The prior distribution selected for the response rate was a beta distribution with parameters α=2, β=3, corresponding to a mean of 40% and a 90% credible interval of 10% to 75%

The table below summarizes a simulation study evaluating the probability that the trial will be halted early under several possible values of the true toxicity and efficacy rates.

True Toxicity Rate	True Response Rate	Probability Trial is Stopped for…	
		Toxicity	Futility
20%	22%	14%	36%
20%	33%	14%	12%
20%	44%	14%	3%
30%	22%	37%	31%
30%	33%	43%	8%
30%	44%	43%	2%
50%	22%	87%	10%
50%	33%	95%	3%
50%	44%	96%	1%

17.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

The primary endpoint of the study is the rate of confirmed 12-week PSA response rate (defined as at least 50% decline from baseline PSA), with confirmatory PSA at least 3 weeks following.

In secondary analysis, the sample mean and standard errors of the time to radiographic progression after the treatment will be summarized, and the post-treatment radiographic response rate together with its 95% confidence interval will be reported. In exploratory analysis, the pre- versus post-treatment measurements, including gene expression, tumor immune microenvironment measurements, immunologic markers, and cytokine

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levels will be compared using paired-t test and Wilcoxon signed-rank test. False discovery rate will be considered to control for multiple testing.

Overall Survival: Survival will be measured as the period from enrollment until death due to any cause or last follow-up. Overall survival curves will be generated using Kaplan-Meier methodology.

Time to Subsequent Therapy: The interval between enrollment and the date of documented initiation of next therapy.

Time to clinical and Radiographic Progression Free Survival: The interval between enrollment and the date of documented clinical or radiographic progression. Clinical progression is defined as increasing symptomatic bone metastases or clinical deterioration due to cancer per investigator's opinion. Radiographic progression-free survival (PFS) is defined as the time from enrollment to documentation of radiographic progression in soft tissue by Investigator's assessment according to RECIST v1.1, in bone according to PCWG3, or death, whichever occurs first. Progression free survival curves will be generated using Kaplan-Meier methodology.

Time to Serological Progression Free Survival: The interval between enrollment and the date of documented PSA progression. Progression will be declared if patient has documented to have a testosterone less than 50 ng/dL. In cases where a testosterone level has not been obtained and patient has not had an orchiectomy, PD will be deemed if patient had a documented rise in PSA on LHRH analogue therapy. Progression free survival curves will be generated using Kaplan-Meir method.

17.3 Sample Size and Power

The null hypothesis is that the true response rate is 0.22 (ARN-509-001, NCT01171898), and the alternative hypothesis is that the true response rate is 0.44. If there are 14 or more responses among these 31 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields the power of 0.80. We will therefore plan to enroll up to 34 patients to account for 10% dropout.

17.4 Data Monitoring Committee

Institutional support of trial monitoring will be in accordance with the FHCC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCC Scientific Review Committee (SRC) and the FHCC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.
Additionally, scheduled meetings will take place biweekly and will include the Principal Investigator (Ruben Raychaudhuri, MD), research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.

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During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

17.5 Exploratory Analysis

In correlative studies we will characterize the pre-treatment TNF-α serum levels and tumor AR-activity score (outcomes) between the clinical responders and non-responders (exposure), defined as at least a 50% decline in PSA from baseline or PSA50. Initially, we will use the Mann Whitney U test and Fischer exact tests to compare the means of continuous variables (TNF-α concentrations) and frequencies of categorical variables (rate of AR-signature classification), given the relatively small sample size. Multiple testing will be corrected by the Benjamini-Hochberg method to control for false discovery rate. To investigate the association between several predictors and clinical response, we will use logistic regression. The core logistic regression model will regress clinical response and pre-treatment TNF-α concentration, with confounders age, race/ethnicity, baseline PSA, and volume of disease. Subsequent models will incorporate pre-treatment and change in AR-activity gene expression scores and additional pro-inflammatory factor concentrations. Our goal is to develop a clearly defined classifier via logistic regression modeling that will give insight into plausible mechanisms underlying any observed associations. In addition, we will explore, using 12-week PSA level as a continuous outcome, whether predictive methods (e.g., random forests or LASSO regression) provide substantially improved prediction over analytic regression models.

18.0 DATA MANAGEMENT/CONFIDENTIALITY

As the Sponsor-Investigator of the Study, Dr. Ruben Raychaudhuri shall be solely responsible for complying with required timelines, any safety-reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations.

Subject research files are stored in a secure place (or database). Access is restricted to authorized personnel.

This study has been designated as an interventional study. As such, all adverse events, special situations including pregnancies and product quality complaints will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of the product under study within the study. All subsequent AEs and SAEs will be collected after this period if the Principal Investigator considers the AE/SAE to be causally- related to the use of the study drug.

For the purposes of this study, the Janssen interventional product(s) are: apalutamide and golimumab.

19.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the Fred Hutch/UW/SC Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, Fred Hutch Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB

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reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these committees and other institutional, state, and federal guidelines.

20.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and oversight of the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The PI must ensure that all subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to undergoing any study-related procedures.

21.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

21.1 Documentation

The documentation of clinical data must be stored by the IND Sponsor according to legal requirements. The PI and study staff are responsible for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the IND Sponsor (if applicable), the FDA, and/or other applicable regulatory agencies at any time, and should consist of the following elements: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the FDA (as needed), IRB, site, and IND Sponsor (if applicable)); and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

21.2 Access to Source Data

The PI will permit the Cancer Consortium representatives or, if applicable, IND Sponsor's representatives, to monitor the study as frequently as deemed necessary to determine that protocol adherence and data recording are satisfactory. The CRF/eCRF and related source documents will be reviewed in detail at each site visit. Only original source documents are acceptable for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the CRF/eCRF, such as past history, secondary diagnoses, and concomitant medications. Other study records, such as correspondence with the IND Sponsor, IRB, and other committees, as well as screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of the FDA or other regulatory agencies.

21.3 Data Collection

Electronic case report forms must be completed and submitted for each subject enrolled in the study. Any changes or corrections made to the CRF/eCRF must be subsequently reviewed and signed by the PI. All data fields in the CRF/eCRF must be completed to avoid queries.

21.4 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB approval and FDA authorization to proceed (if applicable). The IND Sponsor is responsible for submitting protocol amendments to the FDA as described in 21 CFR § 312.30 (Protocol Amendments) and other regulatory agencies according to national, state, or local requirements.

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21.5 Disclosure of Data/Publication
Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by the FDA or other regulatory agencies, the IND Sponsor or its designee, and by the IRB.

21.6 Ethical Considerations
The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the ICH E6 (R2) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, the IRB and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

21.7 Informed Consent
The PI assumes the responsibility of obtaining written Informed Consent for each subject before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or parents/legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The IND Sponsor or designee will review the informed consent prior to submission to the IRB. The form is to be signed and dated by the subject or subject's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the IND Sponsor or designee (if applicable) and approved by the IRB prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

21.8 Institutional Review Board
The PI will assure that an appropriately constituted IRB that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH E6(R2) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB for its review and approval.